THE STRUCTURE OF THE PITUITARY STALK AND THE INNERVATION OF THE NEUROHYPOPHYSIS IN THE CAT

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With a summary
Con un resumen en español
Met een Nederlandse samenvatting

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THE STRUCTURE OF THE PITUITARY STALK AND THE INNERVATION OF THE NEUROHYPOPHYSIS IN THE CAT

PROEFSCHRIFT

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A mis padres

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SOME PRELIMINARY DEFINITIONS

entrance area = zona of insertion of the infundibulum into the tuber cinereum.

zona ependymalis = ependymary epithelium lining the cavity of the recessus infundibularis.

zona fibrillaris = layer constituted mainly by pituicyte cells and by great numbers of nerve fibres grouped in parallel bundles which are disposed approximately in sagittal planes.

zona palisadica = external layer of the infundibular wall. This layer is very poor in cells and rich in vessels and fibres of different sorts.

zona lobularis = peripheral layer of the neural lobe, constituted by Herring's light and dark areas („Verdichtungszonen" and „Zwischenstreifen" of Romeis).

zona granulosa = peripheral layer of the ventral wall of the infundibulum, situated between the zona palisadica and the pars infundibularis.

INTRODUCTION

Systematical investigation of the hypophysis with the help of the microscope began in the last quarter of the nineteenth century. Attention was first focused on the glandular part of the hypophysis which as early as 1853 was included by Ecker in the group of the "vascular glands", which later became "internal secretion glands". The discovery of the physiological importance of this part of the gland (Minkowski 1887, Pierre Marie 1891), led to a detailed histological study of the pars distalis. As early as 1910, considerable advances had been made (Schönemann, Benda, Launois, Gemelli). Comparing all this with the state of knowledge of the structure of the pars nervosa, we cannot help noticing that the study of the latter lagged far behind. Indeed, the existence of nerve fibres in the pars nervosa was still contested as late as 1922 (Bailey, Cowdry).

Several factors may account for this relative delay in the knowledge of the structure of the neural part of the hypophysis. The first was the premise that the neurohypophysis was a rudimentary portion of the diencephalic floor without any physiological importance. The second factor is the great difficulty in staining the neurohypophyseal tissue satisfactorily. The discovery of hypertensor substances in extracts of the pars nervosa by Howell (1898) and the observations of Dale (1906), cleared the way for the increase of the histologists' interest in the investigation of the neurohypophysis, but the staining difficulties remained. Following on the re-awakening of interest, the important work of Tello ('12), Pines ('26) and Greving ('26) appeared. Their work may be considered as the last pronouncements of the first of the two periods into which the history of morphological research on the neurohypophysis can be divided.

The first period extends from the beginning of the microscopical study of the hypophysis (Ecker, 1854) to the end of the first world war. Research during this period was mainly done with the Golgi, Cajal and other silver methods. Emphasis was laid on purely morphological aspects: the characteristic cells of the pars nervosa were carefully described by Berkley ('94) and Retzius ('94); numerous nerve fibres were shown to exist and to originate in the nucleus supraopticus by Cajal ('94), Pines ('26) and Greving ('26); colloidal masses were described by Herring ('08) and the termination of the nerve fibres in the pars nervosa was studied by Tello ('12). These trends in morphological research indicate a natural sequence and progress in the efforts to analyze the structural complexities of the neurohypophysis. The histological work done during this

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first period, excellent as it was, represents only the beginning of the difficult path leading to an understanding of the morphology of the neurohypophysis. That much more work in the same "analytical" direction was necessary to approach this goal is evident.

In short, the course of this research changed about 1924. From that time onwards, the analytical approach, which had been dominant in the past, became of less and less importance, and a more synthetic view of the problems came to be preferred. Interest in physiology was aroused too; in fact, "analysis" began to lose way under the combined pressure of the brilliant advance of the physiology and the changed philosophical and cultural atmosphere of the time. Indeed, the analytical direction taken by microscopical anatomy is very strongly influenced by the cellular theory of Schleiden-Schwann, in which the cell, with its double character of morphological and functional unity, is considered as the elementary constructive unity of the organism. In turn, the cellular theory is based on the "additive Gesichtspunkt" of biology, according to which the multicellular organism seems to be from every point of view (morphological, physiological, developmental etc.) the sum of the cells (resp. cell properties) which compose it. This is the conception of Virchow, Hertwig and Verworn.

In the years after the first world war, not only the validity of the cell-theory but also of the "additive Gesichtspunkt" were questioned. As for the first, it was shown that the cell is not the only elementary constructive unity of the organism since some animals and plants are not constituted of cells. Besides, the importance of the intercellular substance (conceived as living substance) was recognized also. As for the second, it has been superseded by the doctrine of totality (ganzheitliche Betrachtungsweise des Organismus). In morphology, these developments have led to a new theory which attempts to take the place of the cellular theory: the "Synthesiologie" or "Theorie der genetischen Systeme" of Heidenhain ('23, '29).

These new conceptions seriously undermined the cellular theory in its original form and loosened its hold over the minds of the anatomists. The influence of the new ideas is patent in the term "hypothalamo-hypophyseal system" which emphasizes the position of the neurohypophysis as part of a higher unity which, in turn, is subordinated to the preservation of the superior entity of the organism. Is is evident that in such a conception, the main issue is the study of the "link" which integrates the parts into systems of progressively higher order. This is exactly the case with the neurohypophysis.

The work of Collin, Oliveira e Silva etc. shows the new trend. Soon afterwards, the histophysiology of the neurohypophyseal colloid becomes the centre of the general attention. Shortly afterwards, the anatomical work is done as a check on the experiments designed to show the physiological importance of the tractus supraoptico-hypophyseus. At approximately the same time, the importance of the blood vessels as a possible link between the hypothalamus and

the hypophysis was discovered; soon the scientists were divided into two groups: the followers of Popa and Fielding ('30, '33), according to whom the venous blood of the adenohypophysis ascends through the pituitary stalk to reach the hypothalamus, and the followers of Wislocki ('37, '38), who claim that the vascular net of the hypothalamus is independent from that of the hypophysis and that the blood-flow descends. A considerable amount of literature dealing with the vascular arrangement of the hypophysis has appeared recently.

Simultaneously with these developments, a new notion was brought forward: the recognition that some nerve cells may exhibit a secretory activity, i.e., that there are nerve cells that, besides their normal function of transmitting the nerve impulse, elaborate and discharge substances which exert influence on a non-nervous substratum. This new function attributed to a part of the nerve cells has been called neurosecretion. The history of neurosecretion began in 1914 (Dahlgren), to be continued by Speidel ('19), but it was Scharrer ('28, '30, '32, '35, '45 etc) who elaborated the doctrine and gave it a firm morphological basis. The ideas of Scharrer won universal acceptance when Bargmann ('49) showed that the chrome alum-hematoxylin-phloxin method of Gomori stains the neurosecretory products selectively not only in the cell-perikaryon (as was the case with earlier methods) but also in their axons, as far as their termination areas in the neural lobe where they seem to collect around the blood vessels. In the last decade, the Gomori method has been applied by a large number of scientists for the study of the hypothalamo-hypophyseal complex, which has resulted in the appearance of many theories containing more speculation than newly-acquired facts.

From the preceding account of some of the most important developments of anatomical research on the neurohypophysis, it can be concluded that the analysis of the form has, almost always, been secondary to some other approach (generally physiological of histophysiological) to the problem. In fact, the very nature of the problem itself has been changed: the problem which faces every modern worker in this field is the nature of the *mechanism* which integrates hypothalamus and hypophysis into a whole capable of working in harmony. To the solution of this problem, the efforts of the majority of scientists will be directed.

Considering that a direct attempt to solve this problem was for us too large an undertaking, we have contented ourselves with more preliminary investigations. One of the results of the somewhat premature change of direction of research is that numerous structural problems concerning the hypothalamo-hypophyseal complex have remained insufficiently known. For example, the exact microscopial structure of the pituitary stalk, the number and extension of the nervous components of the neurohypophysis, the topography of the tractus tubero-hypophyseus, the number of the fibres in the neurohypophysis, etc. Obviously a detailed knowledge of these and other points would lead to a better

understanding of the anatomical substratum of the functional connection between hypothalamus and hypophysis. In the hope of contributing to this, we have kept our work within strict anatomical limits. No reference to hormone transport, chemotransmitters, neurosecretion, histochemistry of the neurohypophyseal colloid etc., will be found here in consequence.

The starting point for this work was the investigation as to whether the hypothalamic innervation of the neurohypophysis is homo- or heterolateral. Indeed, the neurohypophysis being macroscopically a single organ, we became interested in ascertaining whether the areas of termination of the hypothalamic fibres were situated on the same side as that in which they originate, or not. In order to bring this about, it was necessary to study very carefully the topography of the nerve fibres at different levels in the neurohypophysis. In doing this, attention was paid to some related aspects viz., the structural division of the neurohypophyseal wall in layers, which led in turn to a new division of the neurohypophysis. The original scope of this work was thus progressively broadened as items were incorporated which originally were not meant to be dealt with (a process to be expected in work of this nature).

This thesis contains two main parts: a study of the structure of the neurohypophysis in Chapter IV, and an account of the topography of the hypothalamic innervation of the neurohypophysis in Chapter V. In Chapter IV, the neurohypophysis is described as consisting of three layers of tissue disposed concentrically. On the basis of this description, a new division of the neurohypophysis is proposed. The limits of the infundibulum with the tuber cinereum and with the neural lobe are discussed in detail.

Chapter I is a summary of the papers of Brahms ('32) and Gilbert ('35) on the development of the hypophysis of the cat. No personal observations are reported here. It was felt, however, that an account of the development would give the work a firmer foundation. Besides, it was possible in the figures of Brahms to substantiate our findings, based on adult material, that the dorsal wall of the primitive infundibular diverticulum does not contribute to the formation of the neural lobe, which is formed as a relatively late differentiation of the ventral wall of the primitive infundibular diverticulum. This is an important conclusion which needs further work on embryological material.

Chapter II is a description of the morphology of the adult cat neurohypophysis. The somewhat unusual position of our literature survey can be accounted for by the fact that a previous knowledge of the morphology and nomenclature of this subject may contribute to a better understanding of the literature references.

In Chapter V the topography of the tractus tubero- and supraoptico-hypophyseus is described. The fibres of the former are found to penetrate into the neurohypophysis through the ventral, lateral and dorsal lips of the entrance area. This contradicts the earlier scheme of Fischer, Ingram and Ranson ('35), according to which, the tractus supraoptico-hypophyseus runs through the ventral

wall of the infundibulum, whereas the tractus tubero-hypophyseus runs through the dorsal wall.

The termination of the fibres of the tractus tubero-hypophyseus in the zona palisadica is studied in Chapter VI. Numerous formations, capable of intense staining by silver and probably representing nerve terminals, are described in the zona palisadica. These formations have not been reported hitherto in the neurohypophysis of the cat.

Along the entire course of this study, we have been perfectly aware of the long way that still separates us from a thorough knowledge and understanding of the morphology of the neurohypophysis. This was felt with increasing clarity, the closer the work was to its end. At the same time, the number of new problems multiplied. At a certain moment, the disproportion between the problems and the solutions that we could give to them became so great that the usefulness of publishing the work in its present form was questioned. In fact, the very circumstance of bringing to light a considerable number of new questions reassures us that this work has not been done completely in vain.

CHAPTER I

EMBRYOLOGICAL DEVELOPMENT OF THE HYPOPHYSIS OF THE CAT WITH SPECIAL REFERENCE TO THE PARS NEURALIS

The development of the hypophysis of the cat has been lately reviewed by Brahms (1932) and Gilbert (1935). The importance of these contributions cannot be underestimated as they introduce serious changes in the current views on the early development of the hypophysis. A short summary of the work of these authors seems therefore justifiable.

The early development of the hypophysis in mammals is described in most embryology textbooks in the following way: "The hypophysis is formed from two separate primordial parts which unite secondarily. One of these primordia, known as Rathke's pocket, grows in the mid-line toward the infundibular process of the diencephalic floor" (Patten, 2a ed, 1955, p. 525). This statement is subscribed by the Hamilton Boyd and Mossman, Bailey and Miller and Fischel among other textbooks.

There are two implications in this way of conceiving the early development of the hypophysis: firstly, that both primordial regions which will form the organ, are first separated from each other, secondly, that by means of active growing of their substance, both primordia approach each other, meet and fuse.

The careful analysis of the early development made by Brahms and Gilbert has disproved this theory, and has shown the way to a new understanding of the development of the hypophysis. As they point out, it has been shown by earlier embryologists (Mihalkovics, 1877; Minot, 1897; Hochstetter, 1924), that long before the Rathke's pouch or the infundibular diverticulum appears, the region where the hypophysis is going to develop is clearly established. Its limits are the ectoderm of the ventral lip of the anterior neuropore and the anterior end of the oral membrane (fig. 1). It is characteristic of this area, which may be called (following Kingsbury and Adelmann) "the hypophyseal area", that the surface ectoderm is in direct contact with the ventral wall of the neural tube. This contact is so close that in the posterior third of this region it is not possible to ascertain any basal lining interposed between the two layers of tissue. It is now evident that this firm adherence will force the epithelium from the roof of the stomodoeum to follow the floor of the brain in any movement taking place here.

When shortly afterwards the rostral portion of the nervous system bends ventrally and enlarges to form the forebrain vesicle, the hypophyseal area first placed ventrally, is brought down so that it is now directed dorsally. This change leads to the formation of an angle, the walls of which are the ectoderm of the hypophyseal area and the ectoderm of the upper part of the oral membrane (fig. 2).

As the angle between head and body becomes increasingly acute, the stomodeal epithelium is drawn out and makes the hypophyseal angle more acute. At the same time, a luxuriant proliferation of the head's mesenchyma takes place. This mesenchyma grows between the brain wall and the surface ectoderm thus separating one from the other by a progressively increasing distance (fig. 3).

It is very characteristic that the mesenchyma does not penetrate into the posterior third of

the hypophyseal area in the mid-line, that is to say, the part where the adherence between both epithelia is stronger, until late in the development. It is therefore necessary to accept that the close contact between the floor of the brain and epithelium of the stomodeal diverticulum is maintained during the early development of the hypophysis.

Laterally to this area of contact the proliferation of mesenchyma is, on the contrary, very abundant. Consequently, the floor of the brain and the roof of the primitive mouth become separated by a rapidly increasing distance. This mass of mesenchyma constricts the base of the Rathke epithelium in such a way that it is soon transformed in a narrow stalk connecting the lumen of he primitive mouth with the lumen of the Rathke pouch (fig. 4).

We want to draw the reader's attention to the three following points contained in this description:

1. The primordium of the hypophysis appears as a region with a firm adherence between surface ectoderm and floor of the brain.
2. The surface ectoderm of this region (hypophyseal area) is "pinched off" as a result of he rostral bending of the anterior vesicle of the brain. As a result an angle (hypophyseal angle) is formed.
3. The hypophyseal area is partially isolated from the roof of the promitive mouth, owing to the extraordinary proliferation of the head mesenchyma which pushes away both formations.

We believe that these factors account for the early development of the hypophysis, which is quite a different from that, which is usually described. The concepts "evagination from the roof of the stomodoeum" and "evagination from the floor of the brain" are misleading. They are not evaginations, from the point of view of active growing. The evagination-like aspect of the Rathke's pouch must not lead us to consider it as the result of an active process of proliferation of its own epithelium. On the contrary, we have shown that the formation of this pouch is the result of the inter-action of two combined extrinsic processes (extrinsic with relation to the hypophysis itself), namely the rostral bending of the head and the lateral proliferation of mesenchyma. As for the "secondary union" of both primordia we have shown that they are in close contact long before the onset of the Rathke's pouch and that this contact is not broken afterwards.

It is obvious from the previous description that it is not by active growing and development that the primordium of the hypophysis is established. On the contrary, they are extrinsic processes of development and growth — which must be looked upon as responsible for the early development of the hypophysis. It may be said that this organ is determined by the mode of growth of the head (Adelmann, '25).

Since we are primarily concerned with the embryological development of the pars neuralis, a careful examination of the validity of the last concept, the so-called "evagination from the floor of the brain" seems of great interest. An analysis of this concept and a further consideration of the development of the pars neuralis will provide us with the embryological basis of our present investigation.

According to Gilbert, the growth of any particular region in the brain may be measured in two ways: by making reference to the increase in size and by the number of mitotically dividing cells found in that region. These two aspects of growth are obviously closely related. An actively growing region must, consequently, show a certain degree of mitotic activity, which can be considered as a phenomenon of its growth. Obviously, the rapidly growing areas will exhibit a larger number of mitoses than the slowly growing ones. The significance of determinating by comparison the mitotic activity in the sagittal part of the floor of the brain is now clear.

Careful counting of the number of mitoses in the diencephalic floor of cat-embryos made by Gilbert gave different results according to the age of the embryo studied. In young ones (4 mm.) the mitoses were more numerous in the premammillary region than they were within the infundibular or optic regions. In embryos of 5 to 15 mm. mitoses were found to be more numerous in the chiasmatic plate and in the dorsal part of the premammillary region, while they were rare and sometimes totally lacking in the infundibular region, the postoptic lamina and the ventral part of the premammillary region.

Once the mitotic frequency as an index of the growing activity of a certain area has been accepted, the results recorded mean that the prospective neurohypophyseal territory has no important growing activity of its own and — being practically inactive during the development of the hypophysis — it deserves the denomination of "passive area" (Kingsbury, '24).

It is evident from this study that the formation of the infundibular diverticulum cannot be the result of an active process of growth. As Gilbert says, it must be formed at the expense of material belonging to adjacent regions of the neural tube. If this is the case, it is logical to think that both its form and further increase in size are the result of external processes acting upon this inactive area. These external or extrinsic processes are constituted by the topographical changes induced over the whole head by the active transformations of these early periods of development. In order to get a clear understanding of the formation of the infundibular diverticulum a brief analysis of the topographical changes in the cat-embryo seems desirable.

The infundibular region — "passive area" — is placed in the brain floor between two rapidly growing areas, namely the chiasmatic plate and the premammillary area. Both areas exert pressure on the infundibular area as a result of their expansion. The direction of the pressure exerted by these areas changes according to the variations of position, which the floor of the brain undergoes in these stages (see Gilbert). As the chiasmatic plate is swung caudally and the premammillary area dorsally, the direction of the pressure will be from below-above-behind and from above-forward-below. The infundibular region which is not growing, does not exert counter-pressure. The result should be the formation of a wide depression in the infundibular area, but this is prevented firstly by the accumulation and condensation of mesenchyma below the floor of the brain, which already in this stage reduces the space available, and secondly, by the presence of the Rathke' pouch which further diminishes this space. It is now clear that the infundibular diverticulum is formed under the influence of two rapidly growing regions of the brain on a inactive region that lies between them.

The infundibular pocket, already perfectly visible in cat-embryos of 8 mm., is at first directed cranio-caudally (fig. 5). Soon afterwards a rotation takes place, because its direction is ventro-dorsal in embryos of 35 mm. The cause of this rotation seems to be the proliferation of the buccal epithelium which pushes the neural process toward the base of the brain (fig. 6).

We have just seen how the evagination-like infundibular diverticulum is the result of the mode of development of the floor of the diencephalon, and not an active process of growth. Now, a second question arises: if the infundibular area does not have any growing activity of its own, how does it increase in size in the course of the development?

If we consider that mitoses do not exist in early periods nor in later stadia, there is no other possibility left than that material originally belonging to the chiasmatic and premammillary areas comes to be incorporated into the infundibular area. Kingsbury (1940) describes this transference of material (in the dog) in the following manner: "It takes the form however, of a streaming of nuclei from the infundibular ependyma which determines quite a different appearance of the lining of the infundibular recess as compared with the bordering territory. As the nuclei migrate in from the surface, they enlarge and become distinctly clearer, contrasting thus with the characteristic nuclei of the ependyma". Besides it is possible that, at least in part, the entrance of very numerous axons in the infundibular process plays a rôle in the increase of size of the processus infundibularis. We shall refer to it again later.

In the description given above the hypophysis apears to be determined by general processes of development active upon the whole head. Nevertheless, they cannot be reckoned as the only factors influencing the development of the hypophysis. The results of the work of Blount ('32), Stein ('33), Gaillard ('37) etc. using an experimental approach, show that an interaction between the pars neuralis and the pars buccalis takes place. The result of this inter-

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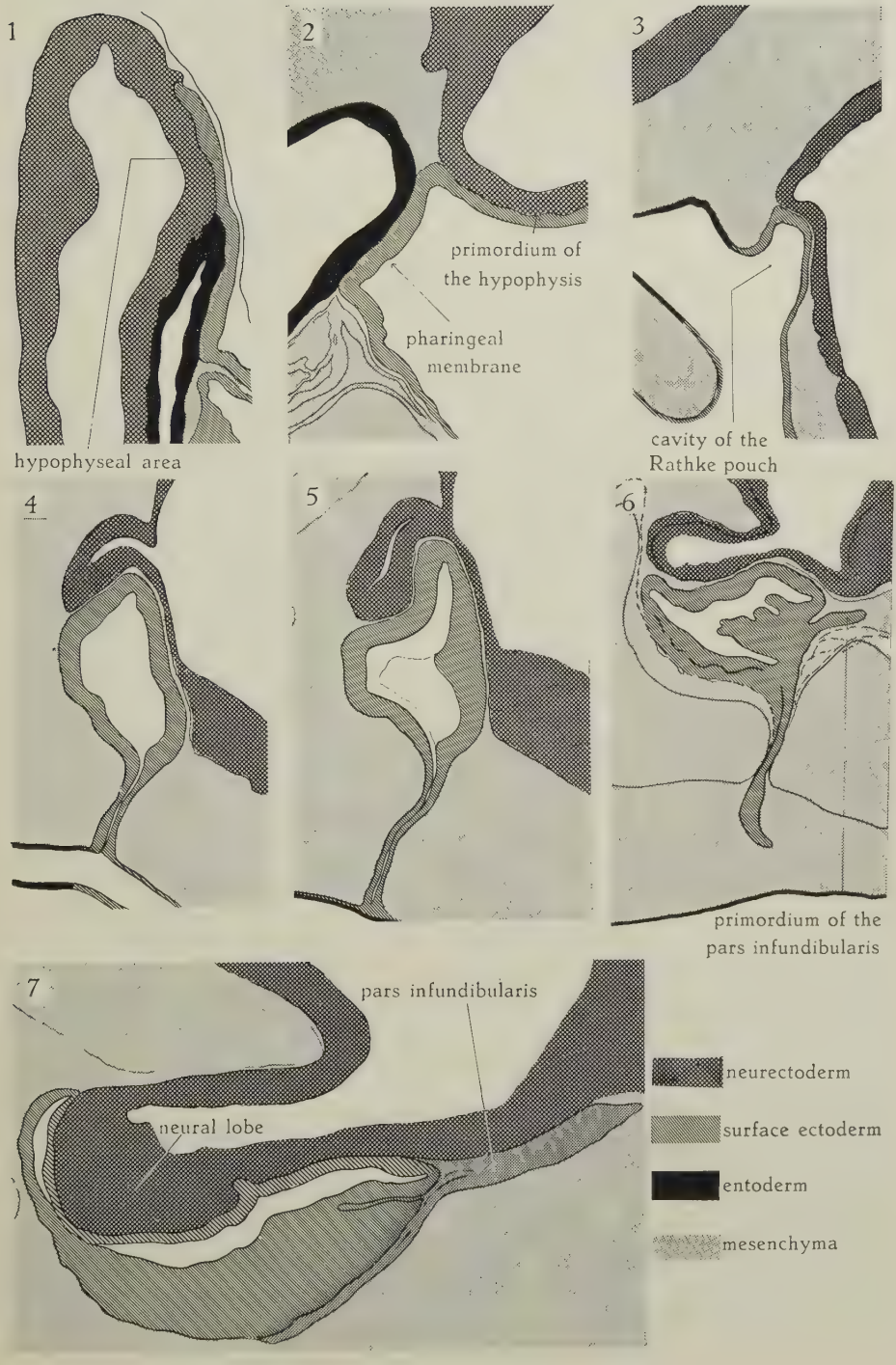
Figs. 1—7. Sagittal sections of the head region of cat embryos from eleven somites to 50 mm of length, showing the early development of the hypophysis (After Brahms, 1932).


1
hypophyseal area
2
primordium of
the hypophysis
pharingeal
membrane
3
cavity of the
Rathke pouch
4
5
6
primordium of the
pars infundibularis
7
pars infundibularis
neural lobe
neurectoderm
surface ectoderm
entoderm
mesenchyma

action is the formation of the pars intermedia which, according to Gaillard, always occurs in the contact area between the infundibular diverticulum and the buccal lobe.

The infundibular diverticulum makes its first appearance in cat-embryos of 5 mm., where it is seen as a slight evagination of the floor of the diencephalon at the apex of the Rathke pouch. The cavity of the third ventricle extends into the diverticulum forming the recessus infundibularis. In early stages (fig. 5-6), the Rathke pouch is closely applied only to the ventral wall of the infundibular diverticulum; the dorsal wall is surrounded exclusively by the mesenchyma. In fact, the Rathke pouch lines also the base of the brain over a rather long extension, reaching up to the chiasmatic plate. Soon, two important changes in Rathke pouch occur. These are the growing of the lateral and posterior investing processes of the pars intermedia + pars distalis and the appearance of the lateral lobes, which in turn, become the pars tuberalis.

After Brahms, in embryos of 14 mm., the lateral investing processes are well-developed and they tend to invest the neck of the neural diverticulum. At the same time, a posterior fold of pars intermedia + pars distalis appears, which grows dorsally, investing the dorsal wall of the infundibular diverticulum. The lateral investing processes of pars distalis and intermedia also grow toward each other along the dorsal surface of the infundibular diverticulum. In 50 mm. embryos, the processes of the two sides are in contact. In this way, the distal portion of the infundibular diverticulum from which the neural lobe originates, comes to be lined by the pars intermedia. It must be remembered that this lining is made up by a fold of pars intermedia + pars distalis, with the narrow cleft of the lumen of the Rathke pouch interposed; much later, both components of the lining fuse together and the cleft disappears. This process of fusion is not invariable but common; when it happens, it is evident that the epithelial investment of the neural lobe consists of fused pars intermedia and pars distalis.

The pars tuberalis appears for the first time in embryos of about 11 mm. as paired outgrowths from the ventrocaudal wall of the Rathke pouch. These lateral outgrowths are directed towards the base of the brain. In its growth towards the diencephalic floor, they are separated from the ventral wall of the pars distalis by a space filled with mesenchyme. The lateral lobes reach the base of the brain in 13,5 mm. embryos. From the distal extremity of each lobe there then appears a hollow ventrally-directed process. These are the ventral horns which in embryos about 17,5 mm. extend as far forward as the optic chiasm. In these embryos similar dorsally-directed processes are seen and these constitute the dorsal horns. The ventral ones grow toward each other and so do the dorsal horns. In 70 mm. embryos both, ventral and dorsal horns are fused. The pars tuberalis is now a collar surrounding the neck of the infundibular diverticulum and closely applied to the base of the brain.

The presence of a prolongation of the lumen of the third ventricle in the infundibular diverticulum allows us to consider this region as formed by four parts, namely, a ventral (basal), a dorsal (cranial) and two lateral ones (fig. 7). The ventral part, continuation of the chiasmatic plate, is a prolongation of the rostral area of the diencephalic floor. The dorsal part of the infundibular diverticulum is a continuation of the mammillary area (dorsal portion of the diencephalic floor). The lateral parts correspond to the rapidly thickening lateral diencephalic walls. It is well known that the lumen of the infundibular diverticulum (the so-called recessus infundibularis) persists in the adult cat, thus maintaining the gross topographical correlation between the different parts of the diencephalon and infundibular diverticulum in the way just mentioned.

In embryos up to 50-55 mm. the ventral and dorsal walls of the infundibular diverticulum are more or less of the same thickness. From then on, the ventral wall of the distal part of the primitive infundibular diverticulum thickens much more than the dorsal one (fig. 7). This is probably brought about by the gathering of material from the chiasmatic plate, as well as by the infiltration of numerous axons arising, for the greater part, in the rostral portion of the diencephalon. This thickening of the ventral wall continues until birth, when the ventral wall is several times thicker than the dorsal one. This thickening gives rise to the future neural lobe; it must be emphasized that only the distal part of the ventral wall of the primitive infundibular diverticulum can be held responsible for this differentiation. The dorsal part does not take part in the forming of the neural lobe.

The enlargement of the lateral part of the neural lobe, as compared with the homonymous parts in the infundibular stalk, is also considerable. It is fairly easy to observe in frontal sections the great difference in size between the lateral part of the stalk and the lateral part of the neural lobe. Probably this lateral growing can be accounted for by the early formation of the sella turcica, which prevents any further elongation of the infundibular diverticulum in a sagittal direction, and the rapid increase in the transverse direction of the head.

CHAPTER II

THE MORPHOLOGY OF THE ADULT CAT HYPOPHYSIS

The hypophysis of the cat is situated in the base of the brain occupying the center of the rhomboidal region limited ventrally by the optic chiasm and optic tracts, which form an angle of ventral convexity, and dorsally, by both pedunculi cerebri, forming an angle of dorsal convexity. The floor of the brain in this rhomboidal region is formed by the tuber cinereum (fig. 15).

When the base of the skull is removed, the hypophysis appears as a pear-like formation hanging from the tuber cinereum, to which it is attached by its narrowest part, the peduncle. The area of attachment of the peduncle lies slightly behind the posterior border of the chiasm. The hypophysis extends dorsally up to the level of emergence of the third nerve, where its dorsal end swells considerably, completely covering the mammillary tubercles which are not visible from below (fig. 8).

Macroscopically, the hypophysis of the cat is made up of two parts, namely, proximal and distal. The proximal part, which has been called "peduncle" in the preceding paragraph, is a whitish, somewhat flat prominence bulging out from the tuber cinereum into which it is inserted. This part is called "median eminence" (of the tuber cinereum) by English and American authors. German authors prefer the name "infundibulum" or "proximal hypophysis".

The distal part is a larger, pink, more or less rounded formation attached tenuously to the other. This part is enclosed in the cavity of the sella turcica (intrasellar hypophysis). The proximal part of the hypophysis is on the contrary, extrasellar, lying in a slightly higher plane.

If we examine with some magnification the zone of insertion of the proximal hypophysis into the tuber cinereum, we observe that a shallow groove appears just at the junction of these two regions. This groove contains some small vessels which make it more visible. It has been called "sulcus tuberis infundibularis" (Spatz, Diepen and Gaupp, 1948) or "sulcus hypophysio-hypothalamicus". The sulcus has the form of a ring encircling the insertion area of the proximal hypophysis in its whole extension. In the dorsal aspect of the proximal hypophysis,

the groove is much deeper than in the rostral aspect.

Further information on the insertion area of the proximal hypophysis in the tuber can be obtained by extirpating the hypophysis as closely as possible to the base of the brain. In doing so, it can be observed that the insertion area has an oval form with the greater axis disposed in the median sagittal plane (fig. 15). The borders of this area enclose a tiny hole which is the entrance to the recessus infundibularis. In the cat a certain space exists between the dorsal border of the chiasm and the rostral border of the insertion area of the proximal hypophysis. This space is called "pars oralis tuberis". Between the mammillary bodies and the dorsal border of the insertion area another space occurs. Spatz and his co-operators call it "pars caudalis tuberis". These spaces show important variations among different vertebrates. In the grown-up man, the pars oralis tuberis is absent. In the rabbit and guinea-pig it is on the contrary more developed than in the cat.

The cat-hypophysis is directed dorsally and slightly caudally, forming an angle of approx. 30° with the base of the diencephalon. In this respect, the cat occupies a position intermediate between man, in which the angle approaches 90°, and the rat and cavia, in which the hypophysis is almost parallel to the base of the brain, the angle tending to become zero. As a result of this position, the sella turcica of the cat is fairly well developed, especially the dorsum sellae which grows very deep and encloses the dorsal (caudal) pole of the neural lobe.

In order to study the topography of the hypophysis with precision, microscopical sections are necessary. In a median sagittal section the proximal hypophysis appears as a thin hollow stem connecting the tuber cinereum with the considerably enlarged intrasellar hypophysis. We note at once that by far the greater part of the neurohypophysis is covered by adenohypophyseal tissue. Only the dorsal (caudal) pole of the neural lobe and a small portion of the dorsal wall of the infundibulum are free of adenohypophyseal lining. It is thus justified to speak of "hypophyseal partners" as Nowakowski does.

The main bulk of the adenohypophysis (pars distalis) is placed rostrally and slightly caudally in relation to the neural lobe. This situation is similar to that found in the human hypophysis in which the pars distalis lies opposite the neural lobe and at the same level. On the other hand, the situation is completely different in the rat, in which species, the pars distalis lies exactly below the neural lobe.

One of the most important peculiarities of the cat neurohypophysis is the existence of an exceptionally long recessus infundibularis which extends as far as the very core of the neural lobe where it stops short showing an enlargement of its lumen. The recessus communicates freely with the third ventricle at the level of the insertion area of the proximal hypophysis in the tuber cinereum. This opening also has an oval form, the long axis being sagittal. The lumen of the recessus infundibularis is limited by a wall consisting entirely of neuro-

hypophyseal tissue. This neurohypophyseal tissue layer shows important differences not only in thickness but also in structure according to the place studied. The neurohypophyseal wall is again lined up by another layer of adenohypophyseal tissue which also shows great differences in structure and thickness according to the level studied.

The presence of the recessus infundibularis causes the neurohypophysis to appear cut in two places in a sagittal (median) section. The whole neurohypophysis is thus divided into a ventral and a dorsal wall. The lateral wall is not visible in this section; in transversal sections it is on the contrary perfectly clear. With low power magnification the enormous difference in thickness between the ventral wall in the proximal neurohypophysis and in the neural lobe is easily noticeable. This is the more striking, since there are practically no differences in thickness between the dorsal wall of the proximal neurohypophysis and the dorsal wall of the neural lobe. The portion of the neurohypophysis of which the walls have approximately the same thickness is called infundibulum. The infundibulum has a particular histological constitution which permits a sharp demarcation with the neural lobe. Its adenohypophyseal partner is the pars infundibularis (the pars tuberalis of English and American literature). In this way, the proximal hypophysis is made up by the juxtaposition of two different structures, one neural (the infundibulum) and the other glandular (the pars infundibularis).

SAGITTAL SECTIONS

In a sagittal section, the infundibulum appears as an elongated hollow tube arising proximally from the tuber cinereum and distally joining the neural lobe. This tube inserts in the base of the diencephalon forming a very acute angle with it. This forces the dorsal wall to make contact with the tuber much earlier than the ventral and hence, the latter is considerably longer than the former. The distance between the implantation of the dorsal and ventral wall in the respective borders of the insertion area represents just the size of the sagittal diameter of the opening of the recessus infundibularis (fig. 8).

The recessus infundibularis — as it appears in a median sagittal section — may be taken as the main axis of the infundibulum. This axis coincides to some extent with the main axis of the hypophysis as a whole. It is situated in a sagittal plane, and is directed dorsally and slightly caudally. Nevertheless, a closer examination of the infundibulum in the neighbourhood of its insertion area in the tuber reveals that this most proximal and small portion of it suddenly makes almost a right angle with the rest. We can thus compare the shape of the cat infundibulum to an L, although the vertical branch is very small in comparison with the horizontal one. Because of this situation the most proximal portion of the infundibulum bulges out, as seen from the plane of the tuber cinereum and we have referred to this on pag. 12 "... a whitish, somewhat flat

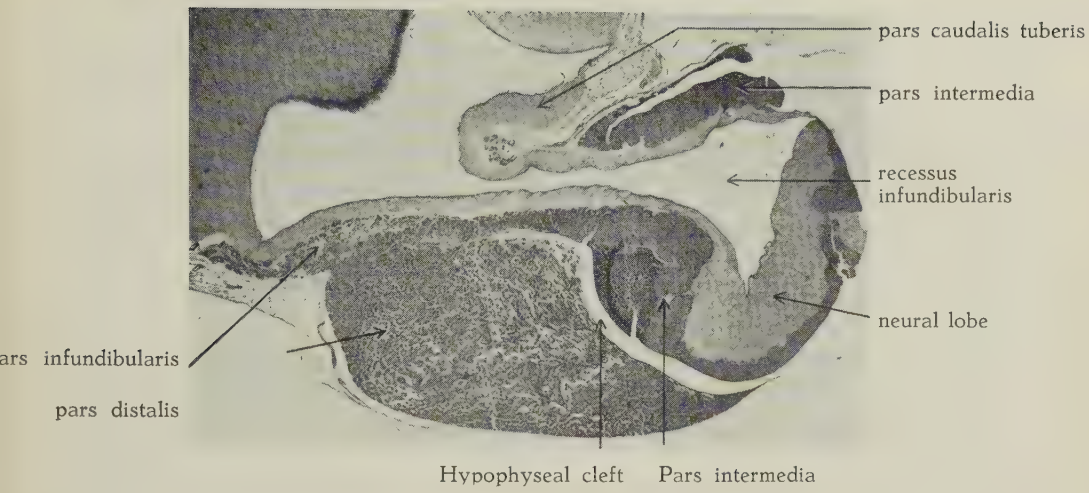


Fig. 8. Median sagittal section of the hypophysis of the cat. Obj. 16 mm. Neg. 8739.

prominence . . .". This is what English and American authors call the median eminence. The median eminence is but a portion of the infundibulum. In the sense of "prominence" this denomination is right, but the whole name (median eminence of the tuber cinereum) implies that this region is a portion of the tuber, which is not true. For this and other reasons, we avoid the use of this term.

The pars infundibularis extends proximally as far as the sulcus tuberis infundibularis, where it stops abruptly. The pars oralis tuberis is thus free from any adenohypophyseal lining. In a median sagittal section, we find the pars infundibularis sectioned twice; the basal part lines the ventral wall of the infundibulum and the dorsal part fills the bottom of the sulcus infundibularis. Here, the pars infundibularis lines not only the dorsal wall of the infundibulum but also the basal surface of the pars caudalis tuberis. The ventral (basal) portion of the pars infundibularis increases in thickness along the proximal quarter of the infundibulum; at more distal levels, it wedges itself between the proximal zone of the adenohypophysis and the ventral wall. At this level, it is only a thin strip of pars infundibularis which separates the ventral wall from the "nasale Umschlagzone". Another thin layer of pars infundibularis is placed over the rostral pole of the pars distalis, being separated from this by a certain amount of connective tissue.

At still more distal levels, the infundibulum is lined by the "nasale Umschlagzone", i.e., the transition between pars intermedia and pars distalis which presently becomes typical pars intermedia. At this moment the hypophyseal cleft appears, separating sharply pars intermedia from pars distalis. It is necessary to emphasize that at this level, the infundibulum has a different adenohypophyseal partner, because the pars intermedia takes the place of the pars infundibularis. At still more distal levels, the ventral wall of the neurohypophysis grows enorm-

ously thick; we are thus in the neural lobe (processus infundibularis).

Similar examination of the dorsal wall of the infundibulum tells us that the proximal portion of this wall is lined by the pars infundibularis (dorsal part). As we move towards more distal levels, the pars infundibularis thins out until it disappears (fig. 8, fig. 27). Shortly afterwards, the dorsal wall of the infundibulum becomes lined by the pars intermedia. Attention must be paid to the fact that between the end of the pars infundibularis lining and the beginning of the pars intermedia the dorsal wall lacks any adenohypophyseal covering. At this level, only the mantle-plexus and the pia-mater are in contact with the dorsal wall. This happens over a short distance only.

In a median sagittal section, the dorsal wall of the neurohypophysis does not show any thickening whatsoever. This forms a marked contrast with what has been described in the ventral wall. It is impossible to distinguish between infundibulum and neural lobe in the dorsal wall, at least with low magnification. In very distal levels, however, the dorsal wall grows extraordinarily thin, being reduced almost to the category of membranes (fig. 8). The pars intermedia does not completely cover the distal portion of the dorsal wall which remains naked. This means that the distal pole of the neurohypophysis, that is to say, the transition between dorsal and ventral wall is free of adenohypophyseal covering, being lined only by the pia-mater.

The description given applies to the majority of our series, especially to those belonging to adult cats. In series 1604 (three weeks old cat), however, the dorsal wall of the neurohypophysis at a level corresponding with the neural lobe is not lined by the pars intermedia. The hypophysis of this series is thus in agreement with fig. 180a of Romeis. Series 1140, 1370, 589, 226, 257, 213, etc. show a well-developed pars intermedia covering the dorsal wall of the neurohypophysis. We think that considerable individual variations occur in this matter.

The pars intermedia covers the greater part of the distal neurohypophysis forming a layer 80-110 μ thick. The portion which lies against the transition zone infundibulum-neural lobe shows a considerable thickening, up to 400 μ in one case. It is separated from the pars distalis by the hypophyseal cleft. This space represents the lumen of the primitive Rathke pouch. It has the form of an interrogation mark $\smile$. At both ends of the cleft, a transition zone between pars intermedia and distalis is present. The position of these transition zones has not always been described in the same way; this is probably due to individual variations in the development. The age of the animal studied probably plays an important rôle in the production of these differences. In young cats, the horizontal branch of the cleft is long and the transition takes place almost in the rostral pole of the pars distalis (Romeis, fig. 180b). A fold is here formed between a layer of somewhat transformed pars intermedia and a layer of pars distalis. In adult cats, a fusion of these two layers occurs, resulting in the obliteration of the greater part of the horizontal branch of the cleft which becomes

considerably reduced. At the same time, a thin wedge of pars infundibularis tissue forces itself between ventral wall and pars distalis getting progressively narrower, until it disappears. There is no continuation between the tissue of this wedge and the pars intermedia. The obliteration of the cleft leaves a thin layer of connective tissue which marks the place where it has been. The existence of this wedge of the pars infundibularis, recognized by Tilney, has been denied by Romeis and Brahms.

The distal fold between pars intermedia and pars distalis is also subject to strong individual variations. In fig. 180a of Romeis, the hypophyseal cleft reaches a high level, whereas in fig. 4 of Nowakowski it disappears at a much lower position. Our series are in agreement with Romeis with respect to the distal fold. According to this author, the thin external layer (representing pars distalis) exhibits the histological structure of the pars intermedia in the median sagittal plane.

In a paramedian sagittal section, the topography of the hypophysis shows the following changes: the continuity between infundibulum and neural lobe is interrupted so that the neural lobe appears as a hollow, more or less round formation lined by the pars intermedia over the whole extension. In very lateral sections, the hypophyseal cleft, with its external layer of pars distalis, may encircle the pars intermedia completely. The infundibulum shows clearly that both the ventral and the dorsal wall are separated by a space which is the recessus infundibularis. Both walls unite distally, closing the cavity of the recessus. The distal reunion of these two walls of the infundibulum represents the lateral wall.

The infundibulum of many of these paramedial sections is lined exclusively by the pars infundibularis, of which the dorsal and ventral parts are shown in direct continuation through a band of tissue, which runs along the outside of the lateral wall of the infundibulum. The horizontal branch of the hypophyseal cleft is not present in many of these lateral sections. The distal segment of the dorsal wall of the neurohypophysis (which here forms the roof of the neural lobe) is made up by a membrane much thinner than in more proximal levels.

The explanation of the peculiar interruption of the continuity of the neurohypophysis in parasagittal sections can be found in the special shape of the infundibulum. In sections made parallel to the infundibular axis, it can be observed that it has the shape of a sand-glass, of which one of the broad sides is attached to the diencephalic floor. This means that the infundibulum gets steadily narrower, as the distance to its insertion area increases. Beyond its narrowest point, the diameter of the neurohypophysis suddenly widens and forms the neural lobe which represents the second dilatation of the sand-glass. It is thus evident that in lateral sections we shall find the proximally and distally dilated portions of the neurohypophysis but not the narrow central part. The funnel-like shape of the infundibulum is of importance for a good understanding of the situation

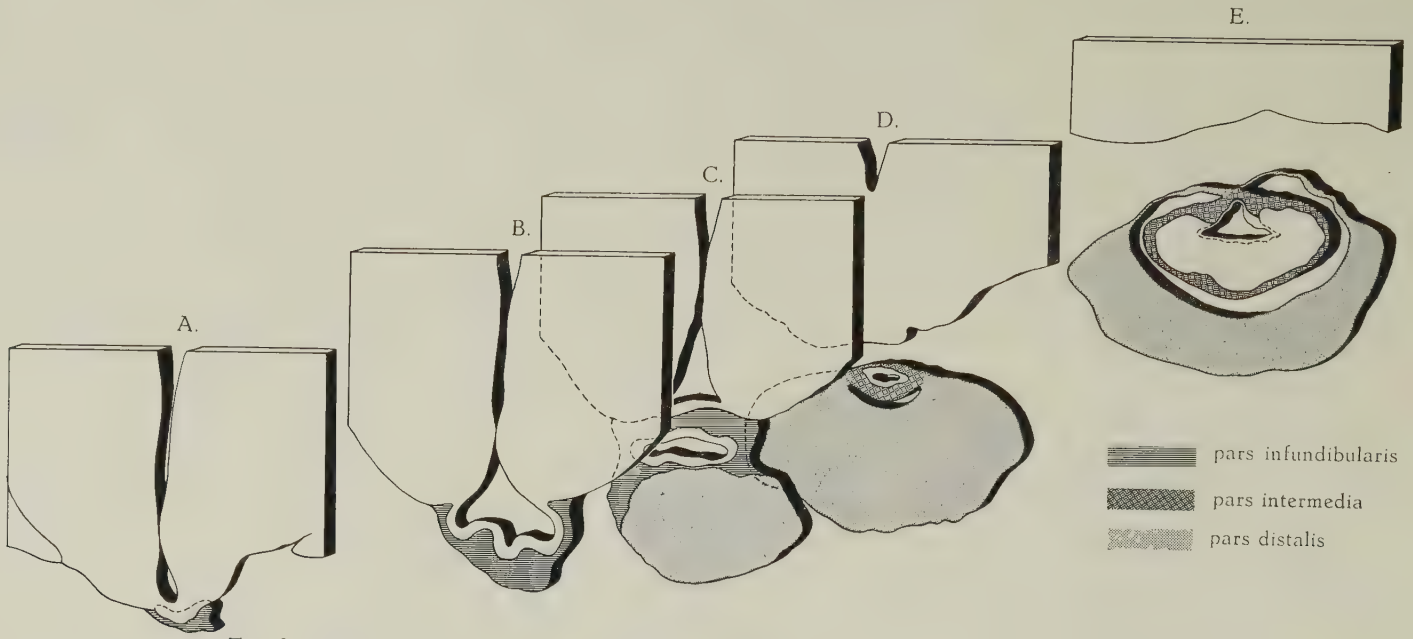


Fig. 9. Section A represents the ventral lip of the entrance area. Section B represents the lateral lip. Note that the neurohypophyseal wall which forms the roof of the neural lobe is extremely thin in comparison with the floor.

of the nerve fibres inside its wall.

FRONTAL SECTIONS

Frontal sections show the infundibulum cut more or less perpendicularly to its main axis and permit a quick and accurate view of its morphology. When comparing proximal, middle and distal sections, we note at once the considerable differences in the transversal diameter which exist at these levels. In fact, the infundibulum is a cone-like shaped organ; authors have long been aware of this since infundibulum means funnel.

As frontal sections of the infundibulum show clear morphological changes depending on the level of the section considered, it will be necessary to record these changes at different levels. We shall proceed from proximal to distal, and consider five sections (see key diagram fig. 9).

Section B. The schematic drawing (fig. 10) shows the position of this section. A glance at the diagram shows already that owing to its shorter length the dorsal wall cannot be present at this level. Accordingly the section shows only the ventral wall, joining the tuber by means of the lateral walls. The sulcus tuberis infundibularis is very clear, its cavity being filled with tissue of the pars infundibularis which ends here. At the bottom the niche-like cavity of

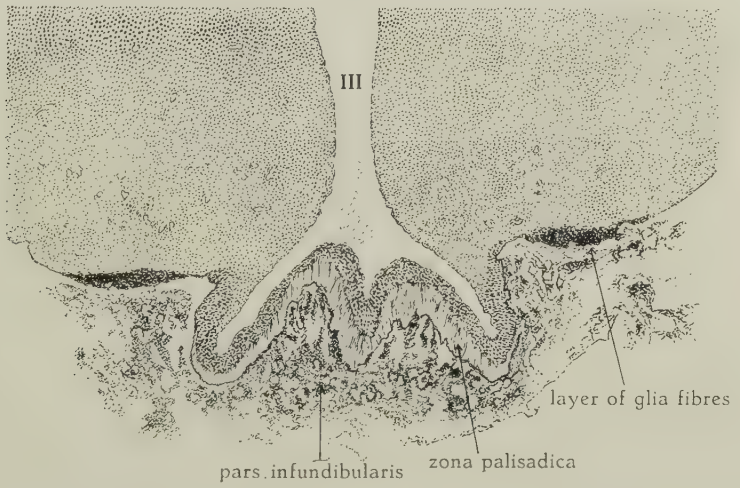


Fig. 10. Frontal section of the infundibulum. Note that the zona palisadica disappears in the lateral lip of the entrance area.

the third ventricle is in communication with the recessus infundibuli. Attention must be paid to the fact that the junction of the lateral wall with the tuber cinereum represents the lateral lip of the insertion area. The ventral lip is not depicted in this figure (see section A of fig. 9).

The ventral wall presents itself as a thin wall divided almost symmetrically into two halves by a clear median groove (fig. 10). Neither the right nor the left half of the ventral wall tend to follow a straight line; on the contrary, they are strongly curved, protruding into the cavity of the recessus infundibularis. This situation can be compared to a tautly strung bow. Thus the floor of the proximal part of the infundibulum is formed by twin elevations, separated by a narrow groove. As such a situation occurs in more than 40 sections, it means that, at least, the proximal 0.5 mm. approx. of the infundibular floor is made of two symmetrically placed ridges separated by a very narrow and deep valley.

The basal aspect of this region is strongly concave, and this concavity is filled by the pars infundibularis of the adenohypophysis which has its maximum thickness here.

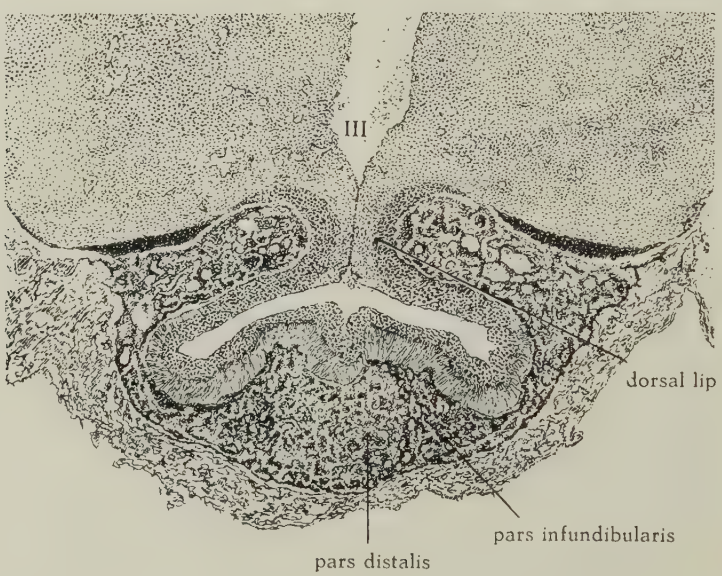


Fig. 11. Frontal section showing the dorsal lip of the entrance area.

The lumen of the infundibulum is obviously affected by this shape of the infundibular floor. Three cavities are formed: laterally, between the lateral wall of the infundibulum and the ridges described, two canals appear, one on either side; in the median line, a furrow distinctly separates the right from the left half of the ventral wall. The recessus infundibularis appears thus trifurcated in this proximal portion of the infundibulum. We give the central groove the name "sulcus centralis infundibuli proximalis".

Section B_1. This section which in fig. 9 corresponds to an intermediate level between sections B and C, already affects the pars caudalis tuberis, where it bends and is transformed into the dorsal wall. For this reason, the dorsal wall joins in the median line a nervous region which is the pars caudalis tuberis

(fig. 11). The section affects the dorsal lip of the insertion area, very close to the dorsal border of the entrance to the recessus infundibularis. At this level, third ventricle and recessus infundibularis are already separated. The walls of the infundibulum completely close the cavity of the recessus which now present an ellipsoid shape, the main axis of which is transversal. The so-called "sulcus centralis proximalis infundibuli" is still very clear. The two lateral ridges are present but not so marked as before. The basal aspect of the infundibulum is still concave; both the pars infundibularis and the pars distalis fill up this space. It can be seen in this fig. how a steadily thinner wedge of pars infundibularis separates the pars distalis from the ventral wall of the infundibulum.

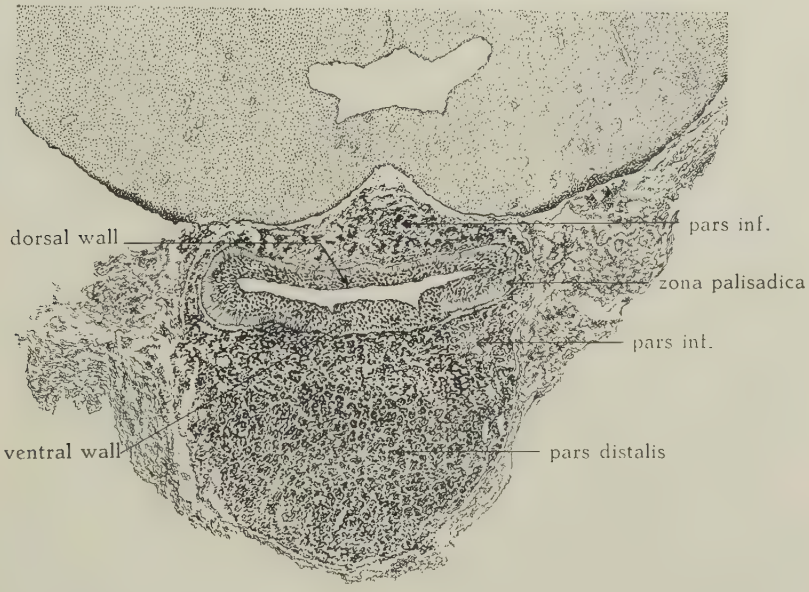


Fig. 12. Frontal section of the hypophysis. The zona palisadica is present in the lateral and dorsal wall of the infundibulum, but not in the ventral one.

The sulcus infundibularis is very marked; it appears as a deep crevice, isolating the dorsal wall from the floor of the tuber cinereum. It is filled with the pars infundibularis which, once the transition zone between dorsal wall and pars caudalis tuberis has been passed, encircles the dorsal wall completely.

Section C. The infundibulum appears now as an ellipsoid organ completely isolated from the diencephalic floor (fig. 12). Its dorsal wall is now separated from the pars caudalis tuberis by the deep crevice of the sulcus tuberis infundibularis. This space is filled by the pars infundibularis which now completely encircles the infundibulum. The lumen of the recessus is limited by the ventral, dorsal and lateral walls, of which the lateral are very small in comparison with the others. At this level, the infundibulum shows its greatest transversal diameter.

The "sulcus centralis proximalis infundibuli" has now disappeared. Instead

two small grooves are occasionally present, but instead of being placed medially, they are lateral (fig. 12). They divide the ventral wall into segments, one central and two lateral ones. As we proceed examining more distal sections, both grooves obtain a more lateral position. Thus, the central segment increases at the expense of the lateral ones which become smaller and smaller.

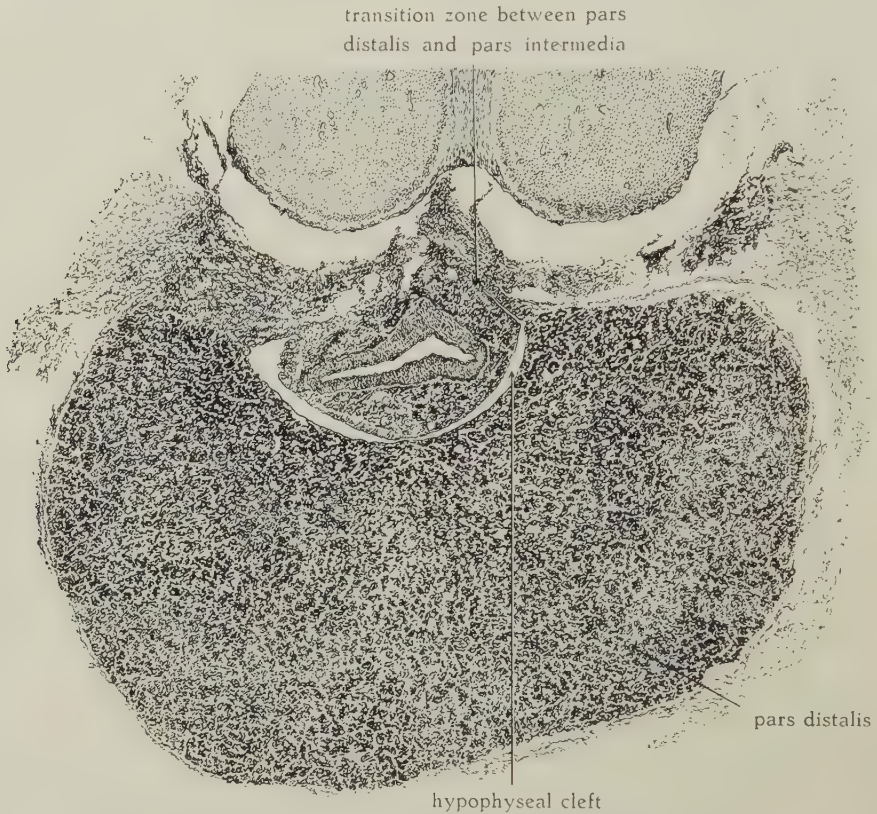


Fig. 13. Frontal section of the hypophysis.

The pars intermedia has not yet appeared. The pars infundibularis is a sort of ring completely encircling the infundibulum. Its thickness is considerably reduced compared with section B, especially in its ventral (caudal) part. This part still separates the ventral wall of the infundibulum from the pars distalis.

Section D. This section corresponds with the narrowest portion of the neurohypophysis, that is to say, it is the neck of the sand-glass. Its diameter is reduced to 1/3 of that of section C. It is worth noting that at this level, the infundibulum shows considerable morphological variations in the different animals studied. Sometimes it has an elliptical form with the main axis transversal, but it may also be almost rectangular (series 1140) with the main axis sagittal. In general the dorsal and ventral wall are approx. of the same thickness. This is not the

case in series 1370 in which the dorsal wall is several times thicker than the ventral one. The dorsal wall may remain almost flat or may show an increasingly sharp angulation (fig. 13); it is also possible that the ventral wall may be bent. Slightly more distally, the structure of the ventral wall changes rather sharply, its thickness increasing enormously which indicates that we are in the neural lobe (processus infundibularis).

The pars infundibularis is no longer visible; in its place the pars intermedia lines the infundibulum. If we study a section corresponding with a slightly more proximal level than this one, we find the small area of the dorsal wall

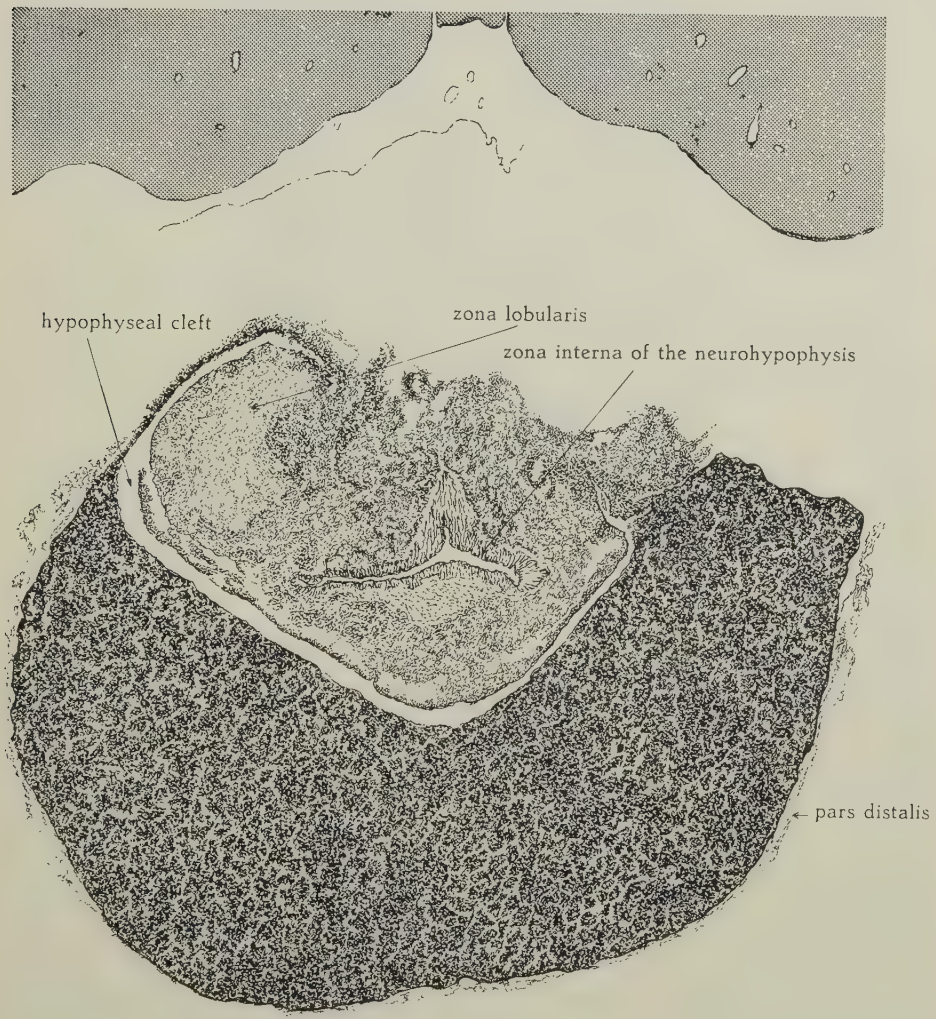


Fig. 14. Frontal section of the hypophysis.

which is not lined by any adenohypophyseal tissue, i.e., the small extension of the wall, in contact with the mantle-plexus and the pia-mater. Section D is already lined by the pars intermedia in all its extension. It must be realised that the thickness of the lining of the ventral wall is much greater than of the dorsal. Numerous follicles are present in the pars intermedia.

The hypophyseal cleft isolates pars intermedia from pars distalis except for the transition zone (distale Umschlagszone) which is situated opposite the lateral wall of the infundibulum. It is worth stressing that the only contact between pars distalis and intermedia is made by these thin bands of tissue which form the transition area (fig. 13). This means that all formations (vessels, nerves) passing from one to the other must follow these narrow connections.

Section E. This last section of the frontal series shows a characteristic change in its morphology. The ellipsoid-like form is now lost; the ventral wall has grown enormously thick in comparison with the dorsal one which is now sharply angulated, the vortex pointing towards the mammillary bodies. The difference in thickness between the two walls is so considerable that the lumen of the recessus now occupies an excentrical situation, being pushed upwards. The lumen itself it also dilated (fig. 9, E).

In the same way as in section D, the pars intermedia lines the processus infundibularis establishing a close contact with it. It is characteristic that, at this level, the thicker area of the pars intermedia is placed against the dorsal wall of the processus infundibularis instead of against the ventral wall, as was the case in section D. The hypophyseal cleft shows the same position as in section D. The pars distalis is smaller in size, since its main bulk lies rostrally to this level. The transition zone pars distalis-pars intermedia can be found close to the median line and leaves a small intermediate space in which the dorsal wall of the neural lobe is only lined by the pars intermedia. In examining still more distal sections, it can be observed that this transition (distale Umschlagzone) takes place much more laterally. At the same time the pars intermedia lining of the dorsal wall of the neural lobe gets thinner and thinner until it dissappears. At this level, the dorsal wall of the neural lobe is reduced to a fine membrane and not lined by any adenohypophyseal partner, but naked.

In several of our series the infundibulum shows, at a level corresponding with that of section D a three-pointed star shape (fig. 14). This may explain certain peculiarities in the appearance of this zone found in sagittal sections. The bulging upwards of the dorsal wall of the infundibulum, with the consecutive increasing of its sagittal diameter, is clearly confirmed in serie 589. In these median sagittal sections, we often noticed that the lumen of the recessus infundibularis is divided into two, in such a way that it sometimes became difficult to tell which was the real one. This was caused by an infundibular splinter originating in the lateral wall of the infundibulum, which according to the direction of the plane of sectioning may be larger or smaller. This splinter is

obviously produced by the obliquely cut lateral wall.

HORIZONTAL SERIES

The pictures obtained in these series depend very strictly on the direction of the plane of sectioning. As the infundibulum has two slight curves, whatever plane of sectioning is chosen, it cannot be seen in its full length in one section.

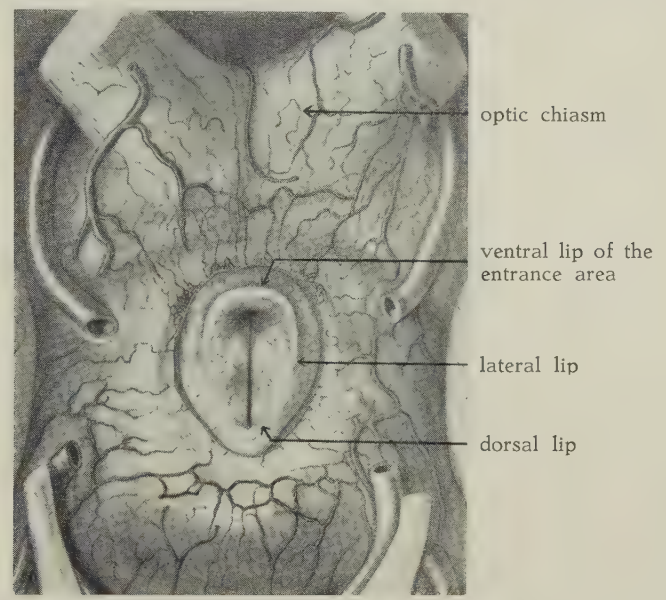


Fig. 15. Basal side of the tuber cinereum. The hypophysis has been removed along the line of its implantation in the tuber. The entrance area is thus exposed (after Wislocki, '37). Neg. 8027.

We should like to draw attention to the shape of the insertion area (= entrance area) of the infundibulum in the tuber cinereum (fig. 15). It can be observed clearly that this area has an oval form, its greater axis being sagittal. We can distinguish here four borders or lips which limit the opening of the recessus infundibularis into the third ventricle. These are, one rostral (= ventral lip), two lateral (lateral lip) and one dorsal (dorsal lip). It must be noted that the lateral lip is considerably longer than the other two and, consequently, it offers a greater "contact area" between infundibulum and tuber cinereum than the dorsal or ventral lips. Thus the lateral lip (thinking in terms of depth we could say also lateral wall) of the entrance area is much more developed than the ventral or dorsal lips (walls).

We have stressed the disposition of the entrance area because a glance at any transversal section of the infundibulum is enough to note the great difference in size between ventral (or dorsal) wall and the lateral one, above all from section B onwards. In most of the infundibulum, the lateral wall is reduced to the

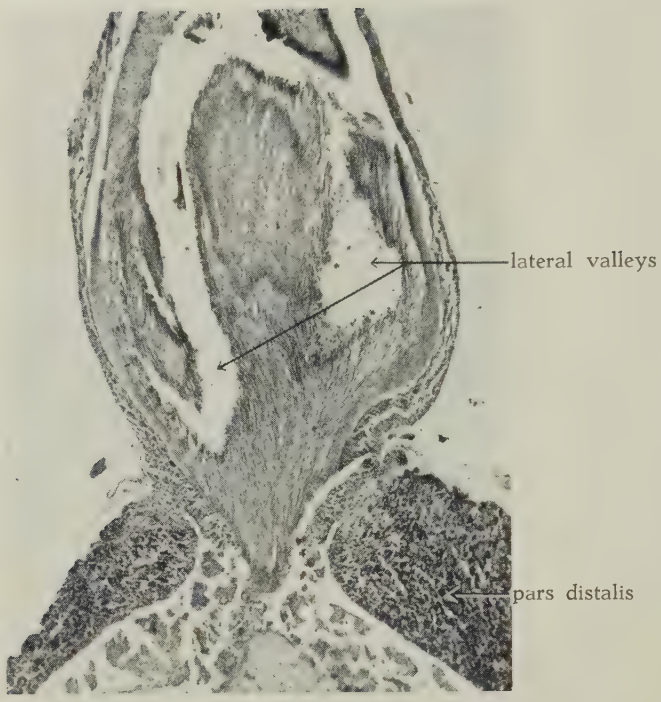


Fig. 16. Horizontal section of the hypophysis. The ventral wall of the infundibulum. Obj. 6,3. Oc. x8. Neg. 6838.

very small portion of the wall laterally closing the lumen of the recessus. As a matter of fact, it would also be possible to speak only of a ventral and dorsal wall in the greater part of the extension of the infundibulum. This can be understood only if we accept that a rotation of the main axis of the organ takes place; by means of this rotation, the sagittal axis of the entrance area changes into tranversal.

The importance of this rotation of the main axis of the infundibulum will become clear in Chapter IV. It will suffice now to say that structures, placed in the lateral lip of the entrance area cannot preserve this situation in more distal levels of the infundibulum owing to the strong reduction of the lateral wall of the organ. These structures must at a certain (proximal) level pass into ventral or dorsal wall.

The topography of the proximal portion of the infundibulum is, moreover, complicated by the sharp upward curving of the ventral (and dorsal) wall which constitutes the short branch of the L (pag. 14). This causes the ventral wall to appear lower than we should expect in horizontal sections.

Horizontal sections of the neurohypophysis over considerable distance may be obtained if the section plane is parallel to the main axis of the infundibulum. In this material the ventral wall can easily be recognized by referring to the

position described on pag. 19. We find the wall in these sections divided into three more or less parallel fragments by two lateral spaces which represent the two lateral valleys of the trifurcation of the lumen of the recessus (fig. 16, compare with fig. 10). The special curvature of the infundibulum causes an island of pars infundibularis to appear often within the median fragment. It can clearly be seen how the transversal diameter of the infundibulum diminishes sharply in its transition zone to the neural lobe, after which, it increases again considerably. The sand-glass form of the neurohypophysis which we have already mentioned, can easily be substantiated in these sections.

Owing to the thinness of the wall of the infundibulum, six consecutive sections may be enough to show important changes. Often it is impossible to distinguish the ventral from the lateral wall, but for applying a histological criterion. In this respect the presence or absence of the zona palisadica (see Chapter IV) may enable us to make this distinction.

The dorsal wall is also easy to recognize in these sections. It appears as a triangular sheet, the base of which is directed against the pars caudalis tuberis. The vortex looks towards the neural lobe. As is the case with the ventral wall, the distal portion is much narrower than the proximal one. It seems to reach the extreme distal region of the neurohypophysis, that it so say, the distal pole of the neural lobe. Often, sections tangential to the dorsal wall show it at its distal part as a narrow strip, soon divided in two symmetrical halves by a faint crevice. This is the result of the angulation of the distal part of the dorsal wall described in pag. 21.

The three-dimensional form of the infundibulum may be seen in fig. 9. We see that it has the shape of a strongly flattened funnel with one of its walls much shorter than the other. With the exception of the insertion area, the lateral walls of this funnel are greatly reduced, owing to the strong vertical flattening of the organ. The ventral wall offers some peculiarities: it is concave, just as if it had been compressed from outside and deeply invaginated towards the lumen of the recessus infundibularis. In two lateral places this invagination is more advanced than in the mid-line. The result is the formation of two lateral canals separated by a ridge, if we look at it from below and imagine the pars infundibularis (which should cover it) removed. If we were able to look at this wall from the side of the lumen, we should then see, a central plateau provided with a median groove (the sulcus centralis proximalis infundibuli). Laterally, the plateau is replaced by two deep canals, the walls of which are formed partly by the ventral wall and partly by the lateral one. This description is valid, when applied to the proximal half of the ventral wall of the infundibulum. The distal half, much narrower, does not present important characteristics. If we could remove remove the roof of the infundibulum, then the floor of the lumen would appear more or less plane.

At its distal end the infundibulum sometimes has a three pointed star shape

or, probably more often, an elliptical form. The dorsal wall is now flexed upward in two halves, forming an angle. This should be the "neck of the sand-glass", already lined by the pars intermedia.

The infundibulum is surrounded for the greater part by the pars infundibularis of the adenohypophysis. The more distal portion of this organ is in contact with the so-called "nasale Umschlagzone" of Romeis and still further, with the pars intermedia. The more distal part of the dorsal wall between the end of the lining of the pars infundibularis and the beginning of the intermedia is only covered by the dura-mater. It is worth remarking that in no case the pars distalis gets into contact with the neurohypophysis.

The nomenclature of the different parts of the hypophysis used in this description is in agreement with that of Spatz, Diepen and Gaupp and Nowakowski with only minor modifications. As this nomenclature differs in some points from that found in other literature, a short summary of it seems desirable for a better understanding of the text.

Embryologically the hypophysis results from the juxtaposition of two different territories: 1. The neural division (neurohypophysis) and 2 The buccal division (adenohypophysis). Topographically, the hypophysis of the cat may be also divided into two parts. These are: 1. The extrasellar hypophysis (= proximal hypophysis) and 2. The intrasellar hypophysis (distal hypophysis).

The extrasellar hypophysis corresponds with what in English and American literature is known as the "median eminence". We avoid the use of this term (see Nowakowski).

The neurohypophysis of the cat may be divided into two portions: the infundibulum (proximal) and the processus infundibularis or neural lobe (distal). The adenohypophysis shows three distinct regions. These are 1. The pars distalis. 2. The pars intermedia and 3. the pars infundibularis (pars tuberalis of English and American literature). We avoid also the use of this term because this region of the adenohypophysis is nowhere in contact with the tuber cinereum.

The proximal hypophysis consists of a neurohypophyseal part (the infundibulum) and its adenohypophyseal lining (pars infundibularis and the "nasale Umschlagzone" and a small part of the pars intermedia).

The distal hypophysis is constituted by the neural lobe and its adenohypophyseal lining (pars intermedia), and the pars distalis, separated from the pars intermedia by the hypophyseal cleft. The disposition in partners of the neuro- and adenohypophysis clearly results from the preceding description.

CHAPTER III

LITERATURE REFERENCES

Anyone conversant with the literature of the morphology of the hypophysis and of the hypothalamo-hypophyseal complex, would distinguish four main categories in which the majority of the work could be classified. These are: 1. Comparative anatomical studies. 2. Descriptive and experimental embryological studies. 3. The histological structure of the hypophysis in normal and experimental conditions and 4. The anatomy and histophysiology of the hypothalamo-hypophyseal complex, i.e., the anatomical basis of the mechanism by which the adenohypophysis is controlled by the hypothalamus or viceversa. In the last decade papers dealing with the last mentioned problem have multiplied beyond measure. Most of these modern contributions are based on the results of the Gomori and other more or less histochemical methods which provide little new information concerning the purely morphological aspects of the problem.

When confronted with the task of giving a survey of the vast literature concerning the hypophysis, one is liable to feel in despair, unless one applies some drastic restrictive criterion. Since we are concerned mainly with the microscopic structure and the topography of the hypothalamic innervation of the cat neurohypophysis, we can eliminate headings 1 and 2. We could have restricted our literature references still further by referring exclusively to the cat, which has been studied in great detail. We have, however, included some of the most important papers on other — not very distant — forms. These papers have been selected because of their importance for a better understanding of the structure, or of the innervation of the neurohypophysis, or of both. Some of these papers have helped us a great deal in clarifying our ideas, viz., Laruelle, Tello, Vázquez-López and Nowakowski.

Microscopical investigation of the hypophysis began probably around 1886 (Lothringer). The early papers dealing with the neurohypophysis are not only of historical importance; often they are full of accurate anatomical data more valuable than can be found in later periods. These papers, in so far as they were available, have also been included.

The scope of our bibliographical survey is thus reduced considerably by the above-mentioned restrictions. Even so, a survey of all these papers is outside the scope of this thesis. We do not claim, therefore, that our bibliographical references are complete.

Retzius (1894) studied the neurohypophysis of the cat using selective neurohistological methods for the first time. He confirmed the earlier observations of Lothringer (1886) besides adding information of his own. He denied the existence of ganglion cells in the processus infundibularis and recognized the existence of nerve fibres and glia cells and fibres. According to him, the nerve fibres terminate showing free ends around the blood vessels of the processus infundibularis.

His illustrations (Tafel XII) show drawings of the neurohypophysis of the cat, dog, rabbit and man. Fig. 1 is a median sagittal section of a cat fetus of 14 cm crown-rump length. Nerve fibres are shown in the ventral and dorsal wall of the processus infundibularis. Nevertheless, the infundibulum is drawn without nerve fibres. The ependyma fibres are very clearly

represented. They originate in the ependymal lining of the recessus and traverse the wall to ramify in several fine branches, which end in the outer limiting layer. Sometimes the cytoplasm of the ependyma cell is not placed in the zona ependymalis but about mid-way in the zona fibrillaris.

His fig. 4 (dog) shows the pars intermedia and a small part of the processus infundibularis next to it. In the pars intermedia, a special sort of cells (ependyma-like) have been stained clearly. In the borderline between pars intermedia and processus infundibularis a thick capillary is present. A mass of neuroglia cells send their prolongations toward the wall of the vessel. No nerve fibres are represented in this figure.

The observations of Cajal (1894, 1904) are extremely important. He demonstrated the nervous nature of a large part of the parallel running fibres which course through the infundibulum towards the neural lobe. Thus he refuted the statements of Henle (1865), Schwalbe (1881) and Kölliker ('86) who defended the glial nature of these fibres. In his "Textura del sistema nervioso del hombre y de los vertebrados" (1904) he says on page 763: "No sólo existe en el lóbulo superior un plexo nervioso, sino que es éste uno de los más ricos, delicados y densos que pueden verse en la substancia gris". And later: "El examen de las secciones longitudinales de la hipófisis permite apreciar que tales fibras terminales son mera ramificación de un manojo de cilindros-ejes que acompañan al pedículo ó infundíbulo, y los cuales, dispersándose en abanico al arribar á una masa gris residente detrás del kiasma óptico, toman origen en numerosas células nerviosas. Muchas fibras se ramifican ya en el espesor del pedículo y acaban cerca de su superficie, mediante cabos varicosos. Del plexo terminal situado en el espesor de la hipófisis, hemos visto salir finas hebras que, introduciéndose en la pared epitelial superior del lóbulo glandular, acaban, mediante ramitos terminales libres y varicosos, entre corpúsculos epiteliales, no lejos de la superficie cavitaria ó glandular de éstos (fig. 643, f)." Thus, besides demonstrating the nervous nature of the fibres, he discovered that these fibres originate in what we call now nucleus supraopticus (pars posterior) and that many of these fibres terminate within the infundibulum, i.e., before reaching the neural lobe. These fibres terminate close to the external surface of the infundibulum. The innervation of the pars intermedia was also described and illustrated by Cajal (figs. 643 and 644 of his book). His observations were made on young mice.

Berkley (1894), described numerous nerve and neuroglia types in the neurohypophysis of the dog, using the Golgi method. The nerve cells were divided by him into two main classes: cells with one neuraxon and cells with two or more neuraxons. Comb-like nerve endings in the processus infundibularis were also described and illustrated by him. In the infundibulum, he pointed at the existence of two layers of different structure: "The outer half of the lamina has fewer nuclei, and a finer as well as a more complicated arrangement of the glia fibrills than the inner, where the component fibrillae are coarser and less complicated, and the nuclei more abundant." With respect to nerve fibres he admitted that they exist in the infundibulum, being the continuity of some fibres of the tuber.

Gemelli (1900, 1906, 1907) has devoted several papers to the study of the histology of the hypophysis. Only his paper of 1906 published in the "Anatomischer Anzeiger", vol. 28, was available to us. In this paper he gives interesting illustrations of the innervation of the pars intermedia. According to Gemelli, numerous nerve fibres concentrate in the border between pars intermedia and neural lobe, where they run parallel to the surface. These fibres have numerous collaterals which penetrate into the pars intermedia where they terminate freely showing endbulbs.

The publications of Herring (1908, 1913, 1914 and 1917) contain very important observations on the structure and development of the hypophysis of mammals. Particularly interesting for us is his paper on the structure of the neurohypophysis of the cat. His description of the morphology of the hypophysis is very exact, as a matter of fact it is the best description that we have found. Special attention should be given to his observation that the dorsal pole of the neural lobe is free from the lining of the pars intermedia and that there is the possibility of a communication between the lumen of the recessus infundibularis and the hypophyseal cleft through this rudimentary area.

The pars infundibularis is described as the "tongue-like process of pars intermedia". Never-

theless, the structural differences between these two parts of the adenohypophysis were not overlooked by Herring: the cells of the "tongue-like process of pars intermedia" are arranged round a central lumen which frequently contains a colloid material. Connective tissue and lymphatics are found between the cell columns, whereas in the pars intermedia sensu stricto the cells are arranged in several layers over the greater part of the body of the posterior lobe. Another important feature which distinguishes these two parts is that the former is very rich in vessels, whereas the pars intermedia is very poorly vascularized.

Concerning the neurohypophysis, he states that the numerous types of nerve cells described by Berkley (1894) are not true nerve cells but neuroglia. He is the first author who speaks of an external and internal layer in the infundibulum. He says "... where there are two very distinct layers surrounding the central cavity, an inner layer in which run longitudinally placed fibres, and an outer layer which is finely granular and apparently traversed by much finer fibres, having for the most part a vertical direction". His further description of the topography of the layers is very accurate. He says on p. 146: "... The finally granular, clear outer layer extends anteriorly to the tuber cinereum, increasing in size as it passes forward. The inner layer of longitudinally running fibres diminishes in thickness, but it is quite well marked where it fuses with fibres and cells of the tuber cinereum. In the posterior lamina (dorsal wall) the two layers are equally distinct, but the longitudinal fibres are fewer in number and both layers become very thin towards their junction with the brain substance in the region of the corpora mamillaria". His fig. 12 is very striking; I think it is the clearest and most complete picture of the structure of the infundibulum that I have ever seen.

Herring's contribution to the knowledge of the structure of the cat-neurohypophysis is marred by important interpretative faults which are the more remarkable if we remember that the material at his disposal must have been excellent. According to him, the longitudinally running fibres in the inner zone of the infundibulum are ependyma fibres and the bulk of fibres in the neural lobe is constituted by neuroglia and ependyma fibres. The source of these errors can be found in his incorrect premise that the Cajal reduced silver method stains the neuroglia and the ependyma. On p. 124 he says: "... Many preparations were made by Cajal silver reduction method which is specially valuable for showing the fibrils of the neuroglia and the ependyma cells of the posterior lobe". Herring must have employed the formules II or III (fixation in pure alcohol or in alcohol-ammonia). Neither the former nor the latter fixation formules stain the neuroglia nor the ependyma at all. In Cajal sections, as his own figures demonstrate, he saw only the nuclei of the ependyma cells and very little, if anything, of the cytoplasm. Furthermore, comparison with Golgi sections should have warned him against confusion between ependyma and nerve fibres, and high power lenses should have told him that the longitudinally running fibres are constituted by bundles of very thin fibres instead of being "much thicker than ordinary non-medullated fibres." According to him these fibres "... clearly arise from cells lining the cavity of the body (posterior lobe) and neck, and pass forwards and upwards towards the brain. They are the fibres of ependyma cells. After a course of varying length, they break up into fine fibrils which enter the outer layer and terminate on its external surface".

Tello (1912) published observations now classic on the human hypophysis using Cajal reduced silver method with previous fixation in pyridine. He concurs with previous authors in denying the existence of nerve cells in the neurohypophysis. On the other hand, the existence of very numerous nerve fibres seems very certain to him. The fibres are thin and delicate, they arrive at the neural lobe through the infundibulum and they run in bundles.

The blood vessels of the neurohypophysis were very accurately described, above all the capillary loops which penetrate into the stalk forming a sort of glomerulus. These vascular formations are less numerous the more we approach the neural lobe. The glomeruli in the stalk ("pars compacta infundibuli" of Romeis) are submerged in a connective mass clearly separated from the rest of the glial and nervous tissue. In many preparations it is possible to see how some fibres penetrate the thick perivascular connective sheath and after splitting and showing local swellings they terminate in small boutons or rings. Concerning the mode of termination of the nerve fibres in the neural lobe, he pointed out that these fibres probably terminate after winding round the vessels.

His account of the degenerative processus undergone by the nerve fibres in the neurohypophysis is of great importance. He says (p. 172): "Las fibras nerviosas que constituyen el abundante plexo de la neurohipófisis presentan con gran frecuencia degeneraciones análogas a las estudiadas en el cerebro por Cajal cuando se interrumpe la continuidad de las fibras experimentalmente, y que, como es sabido, se pueden resumir en la fragmentación de la fibra en una serie de esferas que van perdiendo gradualmente su estructura, hasta queder reducidas á masas pálidas, apenas reconocibles" (see his fig. 10, 11 and 13). Two different phases in the degenerated nervous substance of the nerve fibre are described: the reticular phase, which is revealed as a round disc showing strong affinity for the silver, and the axoplasmatic phase much paler, which surrounds the former. These degenerative processes of the nerve fibres increase with age. The "lesions" should be caused by general pathological agents such as infections, tumors, hemorrhages etc.

Not only degenerative but also regenerative processes occur in the neurohypophysis all the time, i.e., the sprouting of fibres "en massue", similar to those shown by the young growing fibres, the retrograde pathways of many axons, the spreading out of neurofibrillar bundles etc. The newly-formed "massues" may reach very large proportions in some cases, or may appear in the shape of saucers, and their neurofibrills show intense dislocation. The retrograde course of some of these axons should be an important argument in favor of the regenerative character of these processes.

Tilney (1913, 1915, 1936) wrote important papers on the morphology and the development of the diencephalic floor and the hypophysis. His paper of 1913 deals with the pars tuberalis. On p. 260 he states that the neurohypophysis consists of three distinct elements: "namely, the eminentia saccularis of the tuber cinereum, the infundibulum and the infundibular process. The pars buccalis seu glandularis consists of two elements, namely, the pars juxtaneuralis in close relation with and investing the neural portion and the pars distalis, more remote from the neural portion". "Further analysis of the juxta-neural portion of the gland shows that histologically and topographically, it consists of two parts. One of these completely invests the infundibulum and infundibular process, the pars infundibularis. The other part surrounds the eminentia saccularis of the tuber cinereum and because of its close relation to the latter protuberance may conveniently be termed the pars tuberalis".

These statements have exerted a great influence on the division of the hypophysis. It must be noted that Tilney used the term "pars infundibularis" which in his nomenclature corresponds to our pars intermedia. He coined the term "pars tuberalis" which thus far has met with universal approval. It must be said, however, that this denomination is no longer satisfactory. Tilney seems, in this paper at least, to consider the neurohypophysis as a somewhat modified part of the tuber cinereum. He does not seem to have realized that tuber cinereum and neurohypophysis are different things. Hence his statement that the neurohypophysis consists of the "eminentia saccularis of the tuber cinereum", which is a contradiction. Furthermore, since the work of Wislocki (1936) and Fisher, Ingram and Ranson (1938) it is accepted that the "eminentia saccularis" (= median eminence of later authors) must be counted as belonging to the neurohypophysis, i.e., it has the structure of the neurohypophysis, not of the tuber cinereum. It is thus evident that the name "pars tuberalis", originally meant to suggest or to emphasize the close relationship of this part of the adenohypophysis with a part of the tuber, is now inadequate. Since the "eminentia saccularis" (= median eminence) has been identified with the infundibulum by the above mentioned writers and many others (Spatz, Diepen and Gaupp, 1948, Nowakowski 1951, etc.) it is clear that the correct name for this region is pars infundibularis. In fact, as has been shown by the above mentioned German scientists, the pars infundibularis is nowhere in contact with the tuber cinereum. For these reasons, we avoid the use of the term "pars tuberalis".

The subsequent description of Tilney contains highly important observations. He noted that the principal plane of the third ventricle is vertical, whereas the chief plane of the recessus is horizontal. His statement that the pars tuberalis fuses without any line of demarcation with the pars infundibularis (our pars intermedia) is not supported by our observations. He was the first to state that the pars distalis is at no point in contact with the neural portion. Later on he points out the histological characteristics of the pars tuberalis which permit a sharp distinction with he pars intermedia.

Kary (1924) accepts the existence of nerve fibres in the neurohypophysis as proven and tries to determine the origin of the fibres by an experimental approach. If the nerve fibres are axons originated in nuclei of the hypothalamus, retrograde degeneration would occur following a transection of the fibres or a lesion in their sites of termination. In order to get as few operative complications as possible, the buccal approach to the hypophysis was chosen. The neural lobe was destroyed with a thick needle. The animals (young dogs) were killed 12 days after the operation. Frontal series were made of the hypothalamus of these animals which were stained with toluidine blue. She found two different sorts of changes:

1). Intense degenerative phenomena in the nuclei of the cells of the nucleus supraopticus. These changes were pycnosis, formation of vacuoles or enlargement of the nucleus which becomes lighter (less intensely stained). Changes of the cytoplasm in the form of a strong diminution of the Nissl substance which often becomes situated on the border of the cells.

2). The appearance of local glial proliferations spreading over the whole area of the tuber cinereum. Control series were free of these glial proliferations.

These experiments made Kary arrive at the following conclusions: "The so-called basal optical nucleus represents the origin of a system of nerve fibres which enter the neural lobe through the pituitary stalk" (p. 742). In p. 743, she says: "It may be admitted that besides the fibres of the basal optical nucleus, also isolated cells of the central and superior nuclei of the tuber send their axons into the stalk and neural lobe".

Pines (1926) worked mainly on the neurohypophysis of the dog using Cajal reduced silver method. He attempts to answer three questions:

1) Do true nerve cells exist in the neurohypophysis?

2) Are nerve fibres numerous and which are their morphological characteristics?

3) What is the site of origin of the nerve fibres?

The answer to the first question is negative. The cells of the neurohypophysis have no typical axons and Nissl granules and thus, they cannot be considered true ganglion cells. On the contrary, the existence of nerve fibres in the neurohypophysis is an indisputable fact according to him. The fibres are unmyelinated, of great length, they run in bundles which are often longitudinally directed. The isolated fibres split into fine branches which end, showing terminal dilatations. The existence of a rich and closely woven nervous plexus in the neural lobe is out of question, according to Pines.

Studying longitudinal sections which were cut somewhat obliquely, he succeeded in establishing the origin of these fibres. According to him the fibres form a distinct central bundle for which he suggested the name "fasciculus hypophyseus". He could trace the fibres as far as a mass of nerve cells of the hypothalamus situated somewhat behind and above the chiasm. These cells belong to a large nucleus placed laterally, they are large, oval or rounded, possessing one to three dendrites. They are similar to the cells of the nucleus dorsalis nervi vagi. The axons of these cells converge towards the mid-line and run through the infundibulum into the neural lobe. The question whether all fibres of the neurohypophysis belong to this group of cells was left unanswered by Pines. The nucleus from which the axons originate, is to be identified with the nucleus supraopticus, which according to him, had better be called "nucleus hypophyseus".

Stengel (1926) examined the nervous connections between neurohypophysis and diencephalon of the dog and cat by means of the Agduhr method. He reached the following conclusions: "The ganglion cells of the diencephalon send nerve fibres to the neural lobe. Some nerve cells were also found in the latter. The fibres for the hypophysis do not originate on a single nucleus of the diencephalon, but in several. It can be stated that the fibres for the hypophysis originate from small cells placed on the median line in the floor of the third ventricle and also, from a nucleus situated in the anterolateral region of the tuber cinereum which should not be mistaken with the n. supraopticus. The n. supraopticus itself can be considered as the origin of a considerable part of the neurohypophyseal fibres. A number of those fibres originates from a cell group lying medial to the tractus opticus".

Greving (1926) applied himself to demonstrating the existence of nerve fibres in the infundibulum and processus infundibularis. According to him there was an overwhelming amount of literature which claimed that nerve fibres did not exist in the neurohypophysis. Using the Schultze-Stöhr method on obliquely-cut horizontal sections, he succeeded in impregnating a system of fibres placed in the infundibulum, the nervous nature of which was obvious. This system could be traced into the tuber cinereum. In the transition tuber cinereum-infundibulum, the fibres are placed in the periphery, from where they send branches to the more central areas. Often the fibres surround small "islands" constituted by a group of cell nuclei situated around a capillary. Very fine nerve branches issued from the strong neighbouring bundles penetrate into the substance of these "islands".

The nerve fibres of the pituitary stalk have different diameters; the fine show small varicose swellings — which supports the assumption that they are of nervous nature.

This system of fibres could be traced as far as the nucleus supraopticus. In this way, Greving was able to recognize the identity of this bundle as that described earlier by him with the name of tractus supraopticus inferior. In this paper, he proposed the denomination of tractus supraoptico-hypophyseus for this bundle of nerve fibres.

Broers (1933) studied the genesis of the diabetes insipidus by means of experiments. Only a short reference in the Archivio di Scienze Biologiche is known to us. By means of lesions placed in the tuber cinereum, he could produce transient or permanent diabetes insipidus. The neural lobe plays an important rôle in the mechanism of the production of these disturbances. Atrophy of the neural lobe was found twice after bilateral destruction of the nucleus supraopticus. He arrived at the conclusion that the supraoptico-hypophyseal system controls the Na metabolism.

Laruelle (1934) studies the morphology of the vegetative centra contained in the walls of the third ventricle. He deals with four questions: 1. Cellular types and topography of the nuclei of the medial part of the diencephalon. 2. Its fibre connections. 3. The anatomical point of view of the problem of the vegetative localizations and 4. Homologation of the terminology of the vegetative nuclei of the medial diencephalon. His work was made mainly on man, using the Nissl, the thionine and the Reumont silver-impregnation method.

Several cell nuclei may be distinguished in the walls of the third ventricle. The criteria for this differentiation are the following: a) histological type of the cell. b) characters of the "neuropyl". c) topography of the cellular groups in the ventricular wall. d) particular fibre connections of each nucleus. These criteria help to distinguish the following centra: 1. The central gray matter. 2. Supraoptic nucleus. 3. Paraventricular nucleus. 4. Latero-basal nuclei of the tuber. 5. Mamillo-infundibular nucleus. 6. Nuclei of the mammillary body. 7. Nucleus intercalatus. 8. Nuclei of the reticular substance of the hypothalamus. 9. Nucleus reuniens. 10. Nucleus paramedianus.

The fibre-connections of the hypothalamic nuclei can be divided into three groups. These are: 1. Somatic connections. 2. Somatovegetative connections. 3. Purely vegetative connections. Particular attention is paid to the third group. He concurs with the description of Greving. Besides the tractus paraventriculo-cinereus of Greving, there is another fibre connection between this nucleus and the hypophysis. This fibre system descends along the wall of the ventricle to penetrate into the most axial part of the infundibulum where it merges with more peripheral fibres. It follows that the nucleus paraventricularis is connected with the hypophysis by a double system of fibres; one lateral (the tractus paraventriculo-cinereus of Greving) and the other medial.

The fibres of the tractus supraoptico-hypophyseus are thicker and more laterally situated than the other fibre systems. They partly cross the mid-line, being divided into two groups: the first descends along the same half of the infundibulum (stalk), the second, after crossing the mid-line, descends along the other half of the stalk.

The finer fibres originating in the n. paraventricularis also cross the median line but this crossing is placed above the crossing of the supraoptical fibres. He says: "On peut voir, en outre, que certaines fibres venues d'un côté ne descendent pas dans la tige, mais rentrent dans le courant du côté opposé, paraissant constituer un système commissural (fig. 17). A ce système commissural semblent prendre part les fibres fines du paraventriculaire comme les

fibres plus fortes du supraoptique" (p. 832). Confusion with Meynert, Ganser, or Gudden commissures is to be avoided. These commissures do not seem to form part of the vegetative paths of the medial diencephalon.

The innervation of the hypophysis may be summarized as follows: Several fibre systems arrive in the stalk; these are: 1. The tractus supraoptico-hypophyseus. 2. The tractus paraventriculo-hypophyseus, constituted by a lateral group of arched fibres and a medial group of shorter fibres. 3. The tractus tubero-basal-hypophyseus and 4. A fan-like group of fine fibres originating in the central gray matter being grouped closely together in the axis of the stalk. The majority of these fibres are unmyelinated, but there are some myelinated fibres in the stalk which probably belong to the somatic sensitive system.

The commissural systems found by Laruelle in man have been found also by me in the cat (see chapter V). Actually, the degree of the fibre decussation seems to be greater here than it is in man. In the cat, not only supraoptical and paraventricular fibres cross the mid-line, but also fibres from the tractus tubero-hypophyseus which penetrate into the infundibulum through the dorsal lip run to the opposite side.

Sanz-Ibáñez (1934) studied the neurohypophysis of the dog and cat with different staining methods. He could not find nerve cells in the neurohypophysis; on the other hand, neuroglia cells are very numerous. Three sorts of neuroglia cells can be distinguished: the star-like, fusiform and "mousseusses". The latter may be found throughout the whole extension of the neurohypophysis. Those placed in the border line with the pars intermedia are provided with prolongations terminating in small swellings in the contact zone with the pars intermedia.

The fibres of the neurohypophysis belong to three kinds: the nerve fibres, the ependymary fibres and the neuroglia fibres. He stated that the amount of neuroglia fibres is so great that sometimes it is difficult to find the nerve fibres. It is evident that Sanz-Ibáñez mistook nerve for neuroglia fibres. His fig. 9 is very interesting: the termination of the nerve and neuroglia fibres is presented. The nerve fibres are drawn terminating within the internal zone of the infundibulum. Terminations of nerve fibres in the external zone, although not referred to in the text, are also represented.

Ranson and his school have published numerous papers of great anatomical and physiological importance on the diencephalo-hypophyseal system. They used an experimental approach, namely, placing lesions with the Horsley-Clarke stereotaxic instrument in different known areas of the hypothalamus and studying the influence that these lesions exert on the water balance of the animals. Careful histological control, including silver-impregnation methods, were applied. Several papers ('35a, '35b, '38, '39) resulted from this work.

In ('35a) a detailed report on the physiology and anatomy of the experimental cats was given. These experiments have shown that the diabetes insipidus only arises if bilateral injury to the supraoptico-hypophyseal system is present. Destruction of the axons of the tractus causes degeneration of the supraoptic nucleus and paraventricular nucleus (less marked). At the same time, important atrophy of the neural lobe develops. This atrophy consists of enlargement of the cavity of the posterior lobe and of the interglandular cleft. Thinning of the walls of the stalk is also clear. The authors mention that the long processes of the pituicytes and the glial meshwork normally seen in the neural lobe disappear in the atrophic neural lobe. Instead, there were large numbers of elongated, black stained cells without processes.

The lesions were placed so as to interrupt the fibres going through the ventral and lateral lip of the entrance area and were often relatively large. The nucleus hypothalamicus ventromedialis, infundibularis, and part of the lateral hypothalamic area were destroyed by the lesions. In general, the degeneration of the nerve fibres was more marked in the ventral than in the dorsal wall.

We should like to comment on the results of their cat n. 125.: "The chief lesions were in the postinfundibular region, apparently in a position to interrupt the fibres running into the dorsal wall of the stalk. In the ventral floor of the stalk there was a peculiar formation consisting of a skein of what appeared to be myelinated fibres". "The supraoptic nuclei were moderately atrophic probably owing to the interruption of the supraoptico-hypophyseal tract in the region of the skein of fibres just described". We see here an experimental confirmation of our claim that supraoptical fibres also run through the dorsal wall.

According to these authors, destruction of the fibres which course through the dorsal wall of the stalk does not result in marked atrophy of the posterior lobe. The dorsal bundle is smaller and is composed of finer fibres than the ventral tract is, and this fact may account for the apparent absence of atrophy. In cat n. 125, although there was only moderate atrophy of the supraoptic nuclei, the posterior lobe showed greater atrophy than was observed in any other animal; only a very narrow rim of tissue of the pars neuralis remained. Nevertheless, the authors think that this may be an extreme case, especially since in cats with similar lesions (cat n. 90) no such atrophy was observed.

In ('35b) they reported on the result of lesions made on either side of the hypothalamus, an attempt being made to locate the more rostral lesions just behind the optic tract in such position as to interrupt the fibres originating from the supraoptic nucleus — as they loop over the tract and run along the base of the tuber cinereum toward the pituitary stalk. The second lesion, lying caudally and medially to the first, was placed so as to interrupt any fibres which escaped destruction by the rostral lesion. After a period of observation, the animals were killed by bleeding and 1% ammonia in 95% alcohol was injected into the head.

The authors consider the hypothalamo-hypophyseal tract divided into two main nerve bundles. These are: the supraoptico-hypophyseal tract which courses mainly through the ventral wall of the infundibulum, and the tubero-hypophyseal tract which descends along the dorsal wall. In the cats with marked polyuria it was seen that the hypothalamo-hypophyseal tract was almost completely degenerated. Both supraoptic nuclei showed marked atrophy, only a few shrunken cells remaining. The neuro-intermediate lobe showed marked atrophy. It was greatly reduced in size and contained an abnormally large cavity. The interglandular cleft was widened as a result of the shrinkage of the posterior lobe, being filled with colloid. In general it can be said that the lesions influence the fibres in the ventral wall more easily than those of the dorsal one. These results do not impair our belief that an important part of the supraoptical fibres course through the dorsal wall of the infundibulum (see chapter V).

Hair (1938) devoted his efforts mainly to the study of the vegetative innervation of the adenohypophysis of the cat. Since bilateral removal of the superior cervical ganglion does not greatly diminish the number of fibres which enter the pars distalis accompanying the superior hypophyseal arteries, the conclusion was drawn that not all these fibres are sympathetic. He suggested that some of these fibres are derived from the glossopalatine nerve, being thus parasympathetic in origin.

Little information is supplied by Hair concerning the hypothalamic nerve supply of the neurohypophysis. The fibres seem to end either near the blood-vessels (in the neural lobe) or in areas occupied by numbers of pituicytes. In the zone between neural lobe and pars intermedia many of the fibres show terminal enlargements similar to those of the sympathetic fibres in the anterior lobe. The pars intermedia is supplied by an abundance of fibres which originate in the supraoptico-hypophyseal tract.

Some evidence in favor of the innervation of the pars tuberalis by the fibres of the above-mentioned tract was produced by Hair. Unfortunately his fig. 6 is unconvincing: at a magnification of 70, it is almost impossible to see nerve fibres in the zona palisadica. It seems more likely that these formations are ependyma fibres.

Rasmussen (1938) studied the human hypophysis with Cajal and Golgi methods. He was the first to attempt counting the nerve fibres in the infundibulum. He counted 69000 fibres in the adult neurohypophysis. Countings of the cells of the n. supraopticus yielded 70000 cells in the left and 54000 in the right. The two supraoptic nuclei appear to contain twice as many cells as are necessary to account for the fibres that enter the neural lobe.

The innervation of the pars infundibularis is scanty. Only some isolated fibres, which can return to the main bundles of the infundibulum, penetrate into the pars infundibularis. No nerve terminals were observed by Rasmussen in connection with these fibres.

The number of nerve fibres is out of proportion with that of cells present in the processus infundibularis. The relation of the fibres to the pituicytes does not seem to indicate the existence of elaborate morphological dispositives of innervation of these cells other than simple contacts, which, owing to the abundance of nerve fibres are more or less unavoidable. This is against the presumed rôle of the pituicytes as producers of the posterior lobe hormones. Ras-

mussen is inclined to think that these hormones are liberated without the usual aid of secretory cells, as in the humoral mechanisms connected with the sympathetic nervous system

The innervation of the pars intermedia is a poor one. This is at variance with the results of Gemelli ('06), Gentes ('03), Tello ('12), Pines ('26) and Hair ('37). According to Rasmussen, large zones of pars intermedia may be completely free of nerve fibres. On the other hand, in those places where basophilic cells invade the neural lobe, nerve fibres are numerous. Many of the fibres in the pars intermedia seem to be traversing this epithelial stratum rather than terminating there. The proximity of the nerve fibres to the wall of the vesicles seems more incidental than significative. Nevertheless, nerve endings in the pars intermedia occur although in small numbers. Attention was also paid to the vegetative nerve supply to the pars distalis.

Vázquez-López (1942) studied the neurohypophysis of the horse and rabbit. According to him, blood vessels with their accompanying connective tissue, neuroglial cells and their processes and bundles of nerve fibres are the structural elements which together form what may be considered as the fundamental texture of the neurohypophysis.

The connective tissue forms a sort of capsule on the surface of the pars nervosa and inside the substance of the organ it accompanies the blood vessels and helps to form a supporting framework. In the horse, the connective tissue capsule of the pars nervosa is poorly developed along the contact area with the pars intermedia. The contact and communication between the two parts must be regarded as practically uninterrupted. The maximum thickness of the capsule is reached at the tip of the pars nervosa (its dorsal pole) where at one or more points the enveloping pars intermedia disappears and permits continuity with the fibrous dural tissue which lines the base of the skull. In this region, a special sort of corpuscles which he terms "meningeal terminal corpuscles" are found.

Inside the substance of the pars nervosa of the horse, connective tissue is confined to a thin but clear coat of delicate fibres which closely and completely envelops the vessels of medium thickness, and frequently, even the smaller vessels and capillaries. Immediately outside the connective tissue tunic is what may be called a perivascular space, since in ordinary histological preparations it has a hyaline appearance and is relatively devoid of formed elements. This space is particularly clear around the vessels near the pars intermedia. The outer limits of the perivascular spaces are generally sharply outlined by the bundles of nerve fibres which crowd the characteristic substance of the organ right up to the outer limits of the spaces. According to him, this space of variable thickness, devoid of connective fibres and almost totally free of cellular elements is a marked and striking characteristic of the neurohypophysis of the horse.

The nerve fibres are grouped in bundles which occupy the large medial or central portion of the infundibulum leaving a narrower peripheral zone in contact with the pars tuberalis, which is usually described as nearly or completely free of nerve elements. "In reality this peripheral zone (our zona palisadica) contains an abundance of thin fibres which are both differently and less regularly disposed than those of the central area" (p. 8).

Vessels and nerve bundles do not come into actual contact. Around the vessels there is always the perivascular space, the zone which is never invaded by the bundles of nerve fibres which pass along the outside, crowding the tissue substance.

With respect to the third structural element of the neurohypophysis, the neuroglia cells, it is enough to quote the following in relation to the perivascular space: "Closer study shows that the bodies of the neuroglial cells lie closely applied to the surfaces of the nerve bundles. They lie mainly, in fact, upon those surfaces which nerve bundles present to the perivascular spaces and thus, as a single layer, the cell bodies form a diffuse and very incomplete sheet or net stretching round the perimeter of the perivascular spaces". And later "Everywhere processes of neuroglial cells can be clearly seen stretching across the perivascular spaces to end in relation with the vessels, whilst nuclei and bodies of neuroglial cells are found mainly in the areas where the nerve bundles are — seldom, if ever, in the perivascular spaces" (p. 11).

Vázquez-López's description of the nerve endings of the hypothalamic fibres in the perivascular space is truly revealing. According to him, the terminal portions of the nerve fibres in this space assume a completely new morphological character. They begin to twist and turn, becoming contorted and of uneven thickness.

In many respects we are in agreement with this author even in the details as, for example, when he says that the terminal boutons or rings show no particular tendency to aggregate on the vessel wall. His fig. 14 probably corresponds to our "endlamellae". In our material these formations are not so often related to the perivascular space as it seems to be the case in his. Actually it is almost necessary to quote the entire article, so great is the wealth of information. On p. 15 he again refers to the zona palisadica: "In reality this zone is very rich in nerve fibres and nerve endings; they are associated with blood-vessels of the region". And somewhat further: "There is the same wealth of nerve endings apparatus in the perivascular spaces and there is the same tract or sheet formed just within the periphery of those spaces by the very numerous delicate terminal portions of the fibres on their way to points where turning more deeply into the spaces they will assume the character of a nerve ending apparatus".

In his opinion, the greater part of the nerve fibres supplying the neurohypophysis are of sensitive nature, the impulses being thus transmitted centripetally. The relationship between nerve fibres and pituicytes does not support the assumption that these cells are responsible for the production of the posterior lobe hormones as proposed by Ranson and his co-operators.

Green and Harris (1946) have studied the possible ways in which the tuber cinereum (hypothalamus) may influence the pars distalis. The rôle of the vegetative innervation seems to these authors of no decisive importance in the mechanism of this control. Furthermore, the existence of a direct innervation of the pars distalis on account of the hypothalamic fibres seems doubtful, since the majority of the workers in this field admit the scarcity of demonstrable nerve fibres in the parenchyma of the pars distalis. Thus they try to ascertain, if there were other ways by which this influence, demonstrated experimentally, could be revealed. They examined the anatomy of the vascular supply to the hypophysis of rabbits, rats, guinea-pigs, and dogs. Adult human material was also used. Their findings are in agreement with the work of Wislocki (1936, '37, '39). Attention was drawn to the "capillary loops" which must be divided in short and long according to the penetration in the infundibulum. Since blood circulation in the pars distalis is largely independent from that of the neural lobe, it was concluded that control of the hypothalamus could be obtained through the portal vessels linking "median eminence" (= proximal portion of the infundibulum) with the pars distalis. Some experimental evidence supporting this view is produced. With respect to the morphological basis of this theory the following is said: "It is of interest to speculate about the nervous pathways by which the hypothalamus might influence the capillary loops in the median eminence and infundibular stem and so form the first link in a neurovascular chain". Later: "At the moment it cannot be decided which of the above nuclei if any, are linked with the portal vessels. It is possible to state, however, that the capillary loops in the median eminence are surrounded by large numbers of nerve fibres derived from various hypothalamic nuclei, which in turn are connected with the thalamic and subthalamic centres and so with the cerebral cortex and other regions of the nervous system".

Green (1947, '48, '51, '55) has studied the nerve and vascular supply of the hypophysis in many different vertebrates. In his paper of '48, some interesting criteria are given as to the differentiation of nerve fibres from reticular ones. He says: "Nerve fibres were only regarded as such when they showed sharply delimited edges and characteristic decrease in diameter after branching".

The vessels of the primary capillary plexus (he means the "capillary loops" of the infundibulum) are thicker than the capillaries. They are surrounded by a connective tissue sheath which stains as collagen. This collagen is continuous with the collagen of the pars infundibularis. Smooth muscle cells are present in the wall of the vessels. His assumption that Tello mistook collagen fibrills for nerve ones is completely ungrounded.

Besides the connective tissue fibres, the perivascular sheathes also contain cells of various kinds (smooth muscle, reticuloendothelial). He could not identify typical glia cells in the neurohypophysis. Presently he goes on to describe a particular structural zone which he calls "the neurovascular zone", situated in the posterior aspect of the pituitary stalk. This zone seems to be a special area of the pars infundibularis. This zone is sharply demarcated from the infundibulum. It is very rich in collagen. Besides collagen, nerve fibres and blood vessels form the bulk of the zone. "The nerve fibres are derived chiefly from perivascular plexuses of

extraordinary complexity". According to Green, no connection could be seen between the tubero-hypophyseal tract and the zone.

The differences between what he calls "median eminence" or neural stalk and the neural lobe are emphasized. These differences are 1. The blood-supply of these two regions is independent. 2. The vessels which in the "median eminence" and stalk are very rich in connective tissue sheaths, are not found in the neural lobe. 3. The tractus hypothalamo-hypophyseus does not show such elaborate branchings and arborizations in the stalk as in the neural lobe.

In '55 Green studied the hypophysis of rats, cats and opossum with special reference to hormone secretion. Normal and experimental material were used. The latter consisted of rats either deprived of water or artificially overhydrated. He found that in newborn rats, the cytoplasm of certain neural lobe cells was strongly stained. Later on, the Gomori positive material seems to be extracellular, but in animals of two weeks old, it is the same as in the adult. Of interest is the observation that the infundibulum of the rat remained free from Gomori positive material. He says (p. 184): "This is perhaps an unexpected finding, if it is assumed that the Gomori material is being produced in hypothalamic nuclei and is passing through the nerve fibres of the neural stalk to be stored in the neural lobe".

Attempts at producing accumulation of the Gomori material by the administration of posterior lobe extracts, failed. Thirsting produces a clear depletion of this material.

The formation of Gomori material in tissue culture was investigated. Cultures were made of the neural lobes of rats and pigeons. The cells which grew from the explants showed a superficial resemblance to glial cells, and many macrophages with long processes were found growing amongst them. On p. 187 he says: "Material staining with the Gomori chrome alum hematoxylin could be demonstrated in the original explant. It could also be seen in the proliferating cells as the cultures grew older and, in particular, as they began to degenerate".

Cells from young cultures showed no Gomori-like substance. It seems that some degree of degeneration of the explanted tissue is necessary in order to determine the appearance of the Gomori-like substance.

In the "median eminence" numerous granules, visible with the electron microscope, were found inside fibres which are supposed to be nerve fibres. These granules are smaller than those of the neural lobe, and they seem to be intraaxonal. In the neural lobe, on the contrary, the granules seem to be situated extracellularly. The granules are possibly related to the Gomori substance.

Spatz, Diepen and Gaupp (1948) have helped a great deal to clarify our ideas on the topographical distinction between neurohypophysis and hypothalamus. This was very necessary owing to the confusion in the literature on this subject in which the so-called "median eminence" is so often referred to as a part of the tuber cinereum. The article begins as follows: "Das Infundibulum ist ein Abschnitt des Hirnteiles der Hypophyse; das Tuber cinereum ist ein Teil des Hypothalamus". The authors apply themselves to the establishment of the exact meaning of the terms "infundibulum" and "tuber cinereum" which up to now have often been used incorrectly. Rabbit brains were used.

In the rabbit the insertion area of the infundibulum in the tuber cinereum lies at a certain distance from the dorsal border of the optic chiasm. It is worth noting that the axis of the infundibulum in this animal is directed from dorso-oral to ventro-caudal, whereas in man, it is directed to ventro-oral. It can be seen that the infundibulum is separated from the tuber (at the level of the insertion area) by a clear groove which can be recognized macroscopically. They call it "sulcus tubero-infundibularis".

The tuber cinereum, that is to say, the prominence of gray matter forming the hypothalamic basis between optic chiasm and corpora mamillaria completely surrounds the infundibulum. With regards to the implantation of the infundibulum, the tuber may be divided into three parts: 1. The "pars oralis tuberis", situated between optic chiasm and infundibulum; 2. The "pars parainfundibularis", situated around the infundibular insertion and 3. The "pars caudalis tuberis" placed between infundibulum and corpora mamillaria. In man the pars oralis tuberis does not exist, the pars caudalis tuberis, however, is very strongly developed.

The authors then comment on the microscopical series. They are convinced that — at least in the rabbit — no limit can be drawn between "Infundibulum" and "Hypophysenstiel" that is to say, between median eminence and "stem" of English and American literature. The

rabbit's stem (the compact part of the infundibulum) is poorly developed and merges into the neural lobe. Hypophyseal stalk, stem and neural lobe are three portions of one single organ. These three portions together constitute the neurohypophysis in a broader sense. From the developmental point of view these three portions also form a unity.

Despite their close topographical relations, tuber cinereum and infundibulum must be sharply distinguished. The structural characteristics of the latter are the following: In Nissl sections, the infundibulum shows a light staining. A loosely woven glial syncytium may be seen. The layer of glial fibres lining the base of the tuber does not exist in the infundibulum. In silver-impregnated sections, a great number of unmyelinated nerve fibres part of which split up inside the infundibulum itself may be seen. Nerve cells do not count as belonging to the infundibulum; nevertheless, in the frontier between tuber and infundibulum some nerve cells of the nucleus infundibularis penetrate over some distance into the infundibulum.

The sulcus tubero-infundibularis marks on the surface the limit between tuber and infundibulum. It is interesting that this groove is also the proximal limit of the lining of the so-called "pars tuberalis" of the adenohypophysis. It is to be noted that this part does not come into contact with the tuber cinereum anywhere. The so-called "pars tuberalis" is a constant partner of the infundibulum and its proximal end corresponds with that of the infundibulum. The term "median eminence" must be avoided, since it implies that this area is a part of the tuber cinereum. Histologically there is no doubt that the "median eminence" belongs to the neurohypophysis, (infundibulum) and not to the tuber. The term "pars tuberalis" must be rejected, since that part of the neurohypophysis is not in contact with the tuber, but with the infundibulum. "Pars infundibularis" is, therefore, a much more suitable term.

The tuber cinereum is considered as that part of the vegetative hypothalamus (poor in myelin fibres) which bulges outward. The tuber has close relations with the infundibulum, but structurally it must be distinguished sharply from it.

Bargmann and Hild (1949) deal with the problem of the morphological basis of the secretory activity of the hypothalamo-hypophyseal system. Attention is drawn to the investigations of Scharrer and collaborators, which have opened new ground. These authors have reported that histologically demonstrable secretory processes occur in the hypothalamic nuclei. Scharrer has described also a "flow" of secretory droplets along the cell processes of the nucleus preopticus towards the tuber cinereum in fishes.

In order to demonstrate the whole course that the secreted substances follow, it is necessary to find a method which stains these products selectively. This method is the Gomori chromic hematoxylin-phloxin. Bargmann states that with the help of this method, a neurosecretory path extending from the hypothalamus to the neural lobe can be demonstrated.

The nucleus supraopticus of the dog and cat can be seen in Gomori sections with the naked eye, owing to its intense blue staining. Very numerous granuli within the cytoplasm of the nerve cells are seen. It is possible to observe a whole series of secretory stadia, beginning with the nerve cell without granula and with the Nissl substance in the periphery.

The blue-black granula can be demonstrated in the whole extension of the axon. The coarse, swollen cell processes laden with granule masses are very striking. The central part of the axon is stained light red, whereas the periphery is blue-black. In the course of the axon, globular or spindle-shaped accumulations of secretion occur producing the picture of strings of pearls. These accumulations were known as "Herring bodies". They are very frequent immediately beneath the ependyma. With respect to the zona palisadica, Bargmann states: "Der von der Pars tuberalis der Adenohypophyse bedeckte Gliabezirk des Stieles wird nicht der Länge nach von sekrethaltigen Nervenfasern durchzogen. Jedoch begleiten mit kräftigeren Anschwellungen ausgestattete Fasern die durch die Gliazone verlaufenden Blutgefässe, um sich stellenweise mit ihren Verdickungen in das Epithel der Pars tuberalis vorzuwölben".

It could not be ascertained of the fine fibres in the neural lobe release the secretion product in the intercellular spaces. The perivascular spaces, above all those in the neighbourhood of the pars intermedia, show the more intense Gomori reaction. The nerve cells of the nucleus paraventricularis show exactly the same picture after Gomori staining as the nucleus supraopticus. The axons of these cells descend medial to the fornix to reach the nucleus supraopticus. It is impossible to say whether the paraventricular fibres terminate there or continue towards the neurohypophysis.

Rumbaur ('50), deals mainly with the problem of the nerve fibre connections between the diencephalon and the hypophysis. She gives, in the first place, a short survey of the anatomy of the hypophysis of the cat. Her fig. 1 is very important for us; for the first time the recessus infundibularis is drawn surrounded over the whole extension by a layer of tissue consisting of the central zone of the infundibulum. She admits that the neural lobe consists of two zones: one central, which surrounds the cavity of the recessus and is formed by fibres running parallel to the surface of the recessus, and one peripheral. She says: "In den zentralen Teilen, d.h. in den Partien, die den Recessus umgeben, wird das Gewebe von Faserzügen aufgebaut, die zum Recessus parallel verlaufen und sich kontinuierlich in das Inf. fortsetzen bzw. von ihm herabkommen (s. unten). Diesen Teil des L. post. möchte ich mit Merenyi ('48) als "zentrale Zone" des L. post. bezeichnen" (p. 196-197).

We can fully confirm this conception of Rumbaur of a neural lobe constituted by two zones of which the internal is but the prolongation of the zona interna of the infundibulum (see Chapter IV). Her fig. 1 represents a paramedian section of the hypophysis. Nevertheless, she does not mention that in a median sagittal section, the roof of the neural lobe consists of the central zone only.

Rumbaur deals further with the nature, course and characteristics of the infundibular fibres of which the majority are situated in the central zone of the infundibulum, close to the ependyma. They must be considered true nerve fibres and they show typical varicosities in which, under high magnification, neurofibrills can be seen. The thickness of these fibres varies greatly. They run partly in bundles and partly in single fibres. Some fibres of the central zone may change their direction in order to reach the peripheral zone of the infundibulum. They may also penetrate into the rich mass of connective tissue of the pars infundibularis. She estimated the number of nerve fibres, at a level corresponding to the debouchment of the infundibulum in the neural lobe, as being between 15000 and 20000 fibres: "Ich schätze ihre Zahl auf 15-20000". (p. 202).

Concerning the origin of the infundibular fibres, Rumbaur states that the majority of the ventral fibres take their origin from the n. supraopticus. The fibres of the dorsal wall cannot be traced beyond the tuber cinereum. As to whether the infundibular fibres are afferent or efferent, she inclines to the latter view. The termination of the fibres occurs in the neural lobe where they fan out from the zona interna towards the periphery.

The paper by Bodian (1951) is a very successful attempt at elucidating the structural plan of the pars nervosa. He studied the Opossum (Didelphis Virginiana), using a variety of methods (Mallory, Azan, Gomori, Bodian). He considered the lobule as the structural unit which constitutes the neurohypophysis. These lobules consist of a peripheral layer, which he calls palisade layer, where the nerve endings of the tractus hypothalamo-hypophyseus are found, and a central zone made up of the nuclei and part of the cytoplasm of the pituicytes and the pre-terminal segment of the axons of the tractus hypothalamo-hypophyseus. The lobules are separated from each other by connective septa (septal zone), through which the blood vessels penetrate into the depth of the gland.

In the palisade layer, the nerve terminals are parallel to each other, and separated by the branching of the pituicyte fibres. The palisade layer, when stained with the Gomori method, gets a deep blue color. This is due to the coating of the nerve terminals in the palisade zone by a layer of neurosecretory substance which is strongly stained in blue. This would correspond to the "diffuse blueing" of the neural lobe found in higher forms (cat, dog).

In the monkey the structure of the lobule is less clear. His fig. 20 shows a lobule comparable to those of the opossum; the nerve fibres are placed in the centre and they are enveloped by a layer (palisade layer) which, in turn, is encircled by capillaries. His fig. 21 shows what he calls the "inverted" lobule. In this case, the blood vessels occupies the center of the lobule being surrounded by a more or less thick layer of fine, pale nerve fibres (palisade layer) which is limited at the periphery by the bundles of parallel-running hypothalamic fibres (Zwischenstreifen of Romeis). This would seem to be the normal structure of the lobule in higher forms.

Nowakowski (1951) gives the most complete and detailed description of the structure of the cat infundibulum yet available. A detailed survey of this paper is necessary.

Examination of the basal aspect of the diencephalic floor showed that the infundibulum is

separated from the optic chiasm by a certain extension which, in agreement with Spatz, Diepen and Gaupp (1948), he calls "pars oralis tuberis". The implantation of the infundibulum into the tuber cinereum exhibits a clear groove which sharply separates the infundibulum (neurohypophysis) from the tuber cinereum (hypothalamus).

Microscopical examination of the neurohypophysis of the cat makes it possible to distinguish three different portions which he calls "infundibulum", "intermediary portion" and "neural lobe". Each of these parts comes into contact with particular parts of the adenohypophysis by which they are encircled. The infundibulum is the proximal part of the neurohypophysis. The lining of the pars infundibularis is used as landmark indicating the limits of the infundibulum. These are: proximally, the sulcus infundibularis and distally, the distal end of the pars infundibularis. The infundibulum corresponds with what in English and American literature is called "median eminence". In the ventral wall of the infundibulum he notes the existence of a "peripheral zone" poor in cells, in contact with the pars infundibularis and a "central zone", rich in cells and forming the wall of the recessus infundibuli. Surprisingly enough, he continues in this way: "Im dorsalen Anteil des Infundibulum und im Zwischenstück der Neurohypophyse ist eine solche Unterscheidung nicht möglich; hier herrscht das zellreiche Bild der zentralen Zone vor". Our observations are not in agreement with this statement (see p. 56). The fig. 12 of Herring (1908) shows perfectly that the distinction of two zones is also possible in the dorsal wall.

The structure of the insertion area of the infundibulum in the tuber cinereum deserves some attention. All along the perimeter of this area (our "entrance area") cellular conglomerates constituted by nerve cells belonging to the nucleus infundibularis exist. These cells wedge themselves into the infundibular wall over a varying distance (this penetration is greater in the dorsal than in the ventral wall). At this level, the "central zone" of the infundibulum is no longer present, its place being taken by the nerve cell conglomerates belonging to the tuber cinereum. With respect to the "peripheral zone" in this level, Nowakowski himself says: "Am caudalen Anteil fällt auf, dass der Kern von der Pars infundibularis der Adenohypophyse (innerhalb der Sulcus infundibularis) durch eine schmale zellfreie Zone geschieden wird. Diese Zone hat die Charaktere der peripheren Zone des Infundibulum". This statement is not valid for the zona palisadica; in fact, our zona palisadica is not the same as the "periphere Zone" of Nowakowski. (see chapter VI).

The wall of that portion of the neurohypophysis which he calls "Zwischenstück" consists almost exclusively of the central zone. Tissue of the peripheral zone type is limited to "islands" in this region which is surrounded by the rostral transition zone between pars intermedia and pars distalis (nasale Umschlagzone of Romeis) and by the pars intermedia. The neural lobe is constituted by dark and light areas ("Verdichtungszonen" and "Zwischenstreifen"), surrounded by the pars intermedia. Nowhere do neural lobe and pars distalis come into contact.

The fact that there is no "glia externa" lining of the base of the brain in the contact surface between infundibulum and pars infundibularis is stressed. This should be of importance for establishing metabolic interchange between these two hypophyseal partners.

We shall not occupy ourselves with Nowakowski's account of the topography and constitution of the blood vessels of the hypophysis, since they are outside the scope of this thesis. Let it suffice to note that he has explicitly admitted the different vascular disposition of the zona interna of the neural lobe as compared with that of the "Verdichtungszonen" and "Zwischenstreifen". He says: "Wie man auf der Abb. 9 sieht, zieht eine Verlängerung des Mantelplexus (welcher stärker ausgeprägt ist als der Intermediärplexus) in der Hinterlappen hinein. Diese Verlängerung des Mantelplexus, der die Grenze von adeno- und neurohypophysären Gewebe angezeigt hat, bezeichnet hier die Grenze zwischen dem zentralen und dem grösseren peripheren Anteil des Hinterlappens". Similar observations had already been made by Green and Harris ('46) and, in more recent times, by Engelhardt ('56) and Duvernoy ('58). We are in complete agreement with this description (see Chapter VI).

With respect to the nerve fibres, Nowakowski declares that they are unmyelinated and very numerous. According to him, the staining of the nerve fibres in the "peripheral zone" of the infundibulum is by no means easy. Transversally-running fibres lying immediately beneath the ependyma are mentioned by him. The "coarse" nerve fibres of the central zone of the infun-

dibulum can be recognized as the tractus supraoptico-hypophyseus.

Considerable attention is paid to the structure of the peripheral zone. Fibres from the central zone bend sharply entering the peripheral one, where they are difficult to follow. In some cases it can be seen that they terminate in a number of extremely thin and pale branches. The whole peripheral zone is filled with this tenuous, pale-stained nerve plexus which is compared with the "Terminalretikulum" of Stöhr. The author rules out any possible confusion with connective or ependyma fibres; on the other hand, differentiation with glial syncytium is not so easy. On the whole, he himself is inclined to believe in the existence of a plexus of extremely thin nerve fibres stained very pale. The staining of these fibres is very difficult: "Sicher ist, das der nervöse Plexus sehr schwer darstellbar ist und dass man lange braucht, bis man geeignete Präparate erhalt". (p. 298).

In the neural lobe, the fibre disposition is different in the light ("Zwischenstreifen") and in the dark areas (Verdichtungszonen). In the former, the fibres are grouped in parallel bundles. In the latter, they form a plexus of extreme delicacy. This perivascular terminal plexus is easier to demonstrate than the fibres of the peripheral zone.

The Gomori method stains the tractus supraoptico- and paraventriculo-hypophyseus dark blue over the whole extension viz., from the perikaryon of the cell until the terminal arborizations in the perivascular spaces of the neural lobe. On the other hand, the fibres placed in the peripheral zone of the infundibulum and also in the "Inseln" of the intermediary portion remain unstained by this method. Besides, the whole diencephalon remains unspecifically stained (pink) with the only exception of the supraoptic and paraventricular nuclei. In serial sections it is possible to verify that the Gomori positive substance is always located where the fibres of the tractus supraoptico-hypophyseus are situated. It is worth remarking that the territory showing the more intense reaction is the dark areas ("Verdichtungszonen") of the neural lobe, that is to say, the more distal part of the whole supraoptical system.

Bargmann's theory of the transport along the axons of the neurosecretory substances formed in the cell perikaryon is rejected. The author thinks that it is more likely that the neurosecretory substance is produced by the whole nerve cell in its surface: "... könnte es vielleicht auch so sein, dass im ganzen Verlauf des gesamtes Neurons Stoffe an der Oberfläche gebildet werden". According to this theory, the nerve fibres constitute the parenchyma of the neurohypophysis. The pituicytes are reduced to the rôle of mere satellite cells. The want of Gomori positive substance in the pars distalis of the adenohypophysis supports the assumption that no hypothalamic nerve fibres are involved in the innervation of this part of the gland.

Very interesting and important for us are the results of Nowakowski concerning the fibre connection between tuber cinereum and infundibulum. These fibres have been grouped together under the term "tractus tubero-hypophyseus" by Fisher, Ingram and Ranson ('34). These authors claim that this tractus is situated in the dorsal wall of the infundibulum. Nowakowski concurs with this and states that the tuberal fibres may be separated from the supraoptical ones because of the smaller calibre of the former. He saw that fibres originating in the nucleus hypothalamicus ventromedialis converge towards the infundibulum. However, the exact course of these fibres is not accurately reported. A system of descending fibres possibly originating in the nucleus paraventricularis was also noted between the n. hypothalamicus ventromedialis and the wall of the ventricle (this corresponds with our "periventricular system". No mention is made of the commissural fibres of the ventral lip nor of the "palisade fibres" (see Chapter V).

The fibres of the dorsal wall originate in the nucleus infundibularis according to Nowakowski. These fibres are thinner and not so densely aggregated as they are in the ventral wall. These statements are not supported by our findings: in our opinion, supraoptical fibres are numerous in the dorsal wall as the Gomori method shows easily and it is not possible to speak of striking differences in thickness between the axons of the two walls.

Nowakowski concludes that two nerve fibre systems may be distinguished: 1. A Gomori positive system constituted by coarse, long fibres whose origin can be found for the greater part in the nucleus supraopticus and whose termination is the dark areas ("Verdichtungszonen") of the neural lobe and 2. A Gomori negative system, formed by thin fibres originating in the tuber cinereum, the termination of which is to be found in the peripheral zone around the capillary loops of the ventral wall and also, around the "Inseln" of the intermediary portion.

Knoche ('53) analyzed the structure of the zona externa (peripheral zone) in Bielschowsky-Gros, Bodian and Gomori sections. In the central zone of the infundibulum the fibres are thick and coarse. This zone is rich in glial nuclei and in Herring bodies. The peripheral zone is free from Gomori positive fibres and from Herring bodies. The central zone also contains extremely fine fibres which are concentrated in the limit between the two zones. These fibres run parallel to the thick fibres of the central zone. Now and again they run to the peripheral zone where they seem to be in direct continuation with the glial net of the peripheral zone.

A new type of fibre was found by Knoche in the peripheral zone of the infundibulum: that is the "Knötchenfasern". These fibres show thickenings which occur at regular intervals in the course of the fibre. Sometimes only the thickenings are present which, owing to their more or less rectilinear position, help to recognize the existence of the fibre.

Often the "Knötchenfasern" (= beaded fibres) run parallel to the main fibres of the tractus supraoptico-hypophyseus of the central zone, where they may also be present. Confusion with the Gomori positive "Perlschnurfasern" of Bargmann should be avoided.

Hagen ('55, '57) has published very valuable papers on the morphological aspects of neurosecretion and on the structure of the zona externa of the infundibulum under normal and experimental conditions. Only her contributions to the structure of the peripheral zone will be dealt with here. She describes a new layer in the peripheral zone of the dog, which in old animals appears especially clearly. This layer is placed between the pars infundibularis and the peripheral zone. It is rich in vessels and must be reckoned to the peripheral zone i.e., to the neurohypophysis. Very few sharp nerve fibres can be seen in this zone: the majority of them seem to have suffered from a sort of degeneration. Granular products of the degeneration of the nerve fibres are visible. This particular zone has also been seen by Hanström ('52) in the rabbit. This layer is called "zona granulosa". We have also confirmed its existence in the ventral wall of the infundibulum of the cat.

Not only granular remainings of nerve fibres are to be seen in the zona granulosa, but also numerous argentophyle rings (see fig 24 of her paper of '55). These formations are well known symptoms of degenerative processes in the nervous system.

In her paper of 1957, Hagen tries to study the origin and topography of the fibres of the tractus tubero-hypophyseus with the help of lesions placed in the infundibulum of pregnant bitches. The lesions consisted of sectioning the peripheral zone of the infundibulum(!). According to her, the operations were very successful in two cases in which the tractus supraopticus was practically not affected. The choice of the distal part of the infundibulum as site of the lesion seems to us difficult to understand; the peripheral zone grows steadily thinner in distal levels of the infundibulum.

These lesions caused a dark blue granulation of the peripheral zone up to the nucleus infundibularis. Part of the granular fibres of the peripheral zone running parallel to the tractus supraoptico-hypophyseus are identical with the "beaded fibres" ("Knötchenfasern") of Knoche. They might be fibres of the tubero-hypophyseal tract. The lesions caused thus a reversal of the staining properties of the tissue with respect to the Gomori method because neither n. infundibularis nor peripheral zone contain Gomori positive material in normal animals.

The neuroplasm of the nerve cells of the paraventricular nucleus is subject to a foamy, vesicular degeneration after local lesion of the tractus supraoptico-hypophyseus. It can be said that the histology of the diencephalon and neurohypophysis is very variable under normal and pathological conditions.

Brettschneider ('54, '56a, '56b) analyzes the histology of the connections between hypothalamus and hypophysis in several papers. His paper of '54 is concerned with the neurosecretory aspects of the n. supraopticus and paraventricularis. The ending of the fibres originating in these nuclei is also discussed.

In ('56a) he described the nerve fibres in the peripheral zone of the infundibulum of the horse and dog. Great numbers of nerve fibres were found in this zone which, in contrast with the fibres of the central zone, course isolated. The peripheral zone of the infundibulum is separated from the pars infundibularis by a layer of argyrophil connective tissue. It is difficult to say what the origin of the fine, isolated-running fibres of the peripheral zone is. Ac-

cording to the author, these fibres were found already in the transition zone of the tuber into the infundibulum (our entrance area), where they form a bundle. The origin of this bundle cannot be determined with certainty.

A second source of nerve fibres of the peripheral zone are the fibres of the tractus supraoptico-hypophyseus. These fibres leave the tractus bending sharply towards the pars infundibularis. They are darkly stained, showing few swellings. A third group of fibres are those which enter the neurohypophysis accompanying the blood vessels of the infundibulum. These fibres are vegetative. They may be distinguished from the hypothalamic ones because of the many cell-nuclei — probably Schwann cells — which are found along their course. Besides, these fibres are more intensely impregnated by silver than the hypothalamic fibres.

Before ending our literature survey we should like to summarize the present state of knowledge concerning the morphology of the neurohypophysis and its relations with the hypothalamus. From the wealth of information contained in the papers mentioned, four points emerge for further comment: 1., Nomenclature and components of the neurohypophysis. 2., Structure. 3., Hypothalamic nerve supply. 4., The mode of termination of the fibres in the neurohypophysis and especially in the zona palisadica.

1.,The nervous portion of the hypophysis consists of several parts; considerable confusion exists concerning the number and nomenclature of these parts. English and American scientists have almost unanimously adopted the nomenclature of Tilney, modified by Rioch, Wislocki and O'Leary ('40), according to which the neurohypophysis may be divided into: a) the "median eminence of the tuber cinereum"; b) the "infundibular stem", and c) the "processus infundibularis" (neural lobe). Nowadays, this nomenclature and division are widely used. Spatz and his school in Germany have rejected, quite rightly, the term "median eminence of the tuber cinereum". They have strong objections against the words "of the tuber cinereum". In its stead the term "infundibulum" is proposed. Consequently, the term "pars tuberalis" originally meant to convey the idea of the close proximity of this part of the adenohypophysis to the tuber, is to be substituted by "pars infundibularis" which is more in agreement with the facts. The neurohypophysis of the cat has been divided into three parts by Nowakowski: 1. The infundibulum. 2. The intermediary portion ("Zwischenstück"). 3. The neural lobe ("Hinterlappen"). This corresponds with the division of Rioch, Wislocki and O'Leary already mentioned.

Green ('51) has proposed a new division of the neurohypophysis which is based on the topography of its vascular supply. According to Green the neurohypophysis may be subdivided into a) the median eminence: that part which receives its blood-supply from the hypophysioportal circulation or which has a common vascularization with the adenohypophysis. b) the neural lobe: the remainder of the neurohypophysis independently supplied with blood.

The delimitation of the neurohypophysis and the tuber cinereum has been very carefully studied by Spatz, Diepen and Gaupp ('48), Nowakowski ('51) etc. These authors have established that the sulcus tuberis infundibularis, together with the proximal end of the lining of the pars infundibularis mark this limit. Nowakowski has drawn attention to the fact that there is an overlapping of tuber elements into infundibulum and viceversa in the insertion of the latter in the diencephalic floor. The abrupt termination of the layer of glial fibres in the neighbourhood of the beginning of the lining of the pars infundibularis is a further landmark between these two territories.

2. Two structurally distinct layers have been distinguished in the infundibulum. This distinction seems to have been made by Mihalkovicz (1874) for the first time. Later, Berkley (1894) referred to it in passing. Herring ('08) gave a very exact description of both layers which were most clearly represented in his fig. 12. Vázquez-López spoke also of a "cortical zone" and stated for the first time that nerve fibres were present there in great numbers. Finally Nowakowski also made the distinction between internal and external layer, basing it on the difference in cellular density. With respect to the structure of the neural lobe, outstanding contributions are those of Romeis ('40), Vázquez-López ('42) and Bodian ('51).

3. According to Fisher, Ingram and Ranson ('35) the nerve supply of the neurohypophysis of the cat is formed by two great fibre tracts: the tractus supraoptico-hypophyseus and the tractus tubero-hypophyseus. The former is formed by relatively thick fibres which run through

the ventral wall. The latter is constituted by finer fibres originating in different tuber nuclei, and running in the dorsal wall of the infundibulum. Therefore the two fibre systems can be distinguished by the differences in thickness of the fibres and by their respective positions in the walls of the infundibulum.

Nowakowski holds a similar opinion. According to him, the supraoptical fibres run through the ventral wall and the tuberal ones through the dorsal wall. He emphasized that numerous tuberal fibres are situated in the zona palisadica where they terminate. The Gomori method allows a sharp distinction between the fibres of the two great tracts.

4. The termination of the fibres in the neurohypophysis has been especially studied by Tello ('12), Vázquez-López ('42), Hagen ('55) etc. The supraoptical fibres are believed to terminate around the blood vessels of the neural lobe. They may also end as Herring bodies at any level of the neurohypophysis. During the last years it has been observed that a granular disintegration of the nerve fibres in the neural lobe may also occur.

CHAPTER IV

I. THE MICROSCOPIC STRUCTURE OF THE INFUNDIBULUM

After this brief survey of some of the literature concerning the neurohypophysis of the cat, we intend to give in the following pages a summary of our findings concerning the microscopic structure of the infundibulum. This will serve as a sort of introduction to our further description of the topography of the nerve supply of the neurohypophysis. As far as we know, a uniform concept of the structure of the infundibulum does not exist in the literature on the subject. This is due, in our opinion, to the existence of many morphological differentiations which break the structural uniformity of the region. In spite of this, we believe that a single clearly defined structural pattern of the cat-infundibulum can be established.

It is evident that the microscopic picture of a section of the infundibulum must be connected with the plane of sectioning and the staining method used. As to the former, we think that sagittal sections are most informative for a quick appraisal of the structure. As to the staining, it is evident that the nuclear methods will provide simpler pictures. We shall start our description with sagittal sections stained with cresyl-violet.

Ventral Wall. The structure and distribution of the nuclei of the cells constituting the ventral wall can be studied accurately in these sections. With respect to the degree of cellular density of the wall, two layers can be distinguished (fig. 17). The inner one is very rich in cells which form the lining of the lumen of the recessus, which is constituted by a row of nuclei about two in depth. These cells, especially in the proximal part, do not lie close together, so that the lining becomes irregular and half-broken. It may be that in this zone, the liquor cerebrospinalis is in contact with the inner structures of the ventral wall (Collin, '47; Nowakowski, '51; Spuler, '51).

The thickness of the cellular lining is not always the same. Very often, clusters of cells penetrate deeply into the substance of the ventral wall. It is as if the lining of the recessus proliferates in some places, giving thus origin to these islands of cells which remain in contact with the ependyma. Besides there are

many isolated nuclei scattered more or less at random in the thickness of the ventral wall. Sometimes, as is shown in fig. 17, they may show a rather regular arrangement forming a second row of cells parallel to the lining and separated from it by a narrow space. However, they are most frequently placed at random, although they are always more numerous in the neighbourhood of the cellular lining of the cavity of the recessus.

Peripheral to this cellular layer, the cresyl-violet material shows a rather wide

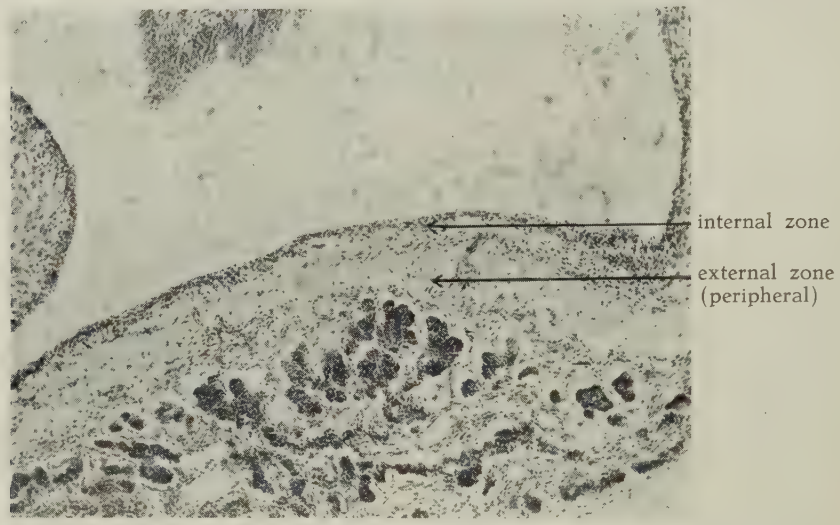


Fig. 17. Sagittal section showing the ventral wall of infundibulum stained with cresyl-violet. Obj. 6,3. Oc. 8. Neg. 6936.

blank space in which it is hardly possible to see even the faintest suggestion of structure. This zone is very poor in cells — a marked contrast with the inner layer. It is traversed by vessels coming from the pars infundibularis (the so-called "capillary loops").

The borderline with the pars infundibularis is not very clear in these sections. Elongated nuclei help to indicate the transition zone between these two parts, although not very clearly.

Dorsal wall. The aspect of the dorsal wall is very similar to that of the ventral one. The nuclei of the cells also concentrated in the border of the lumen of the recessus. The cellular lining seems to be more dense than in the ventral wall, isolating the liquor from the inner structures of the dorsal wall. The lining is 2 — 3 nuclei thick; here also many clusters of cells originating from it grow into the thickness of the wall. (fig. 18).

Peripheral to the cellular layer, exactly as is the case in the ventral wall, there is also a blank space, where we find a faint suggestion of fibrillar structure. This zone is even poorer in cells than its homologue in the ventral wall. It is also traversed by vessels coming from the pars infundibularis. The borderline

Fig. 18. Sagittal section showing the transition between the pars caudalis tuberis and the dorsal wall of the infundibulum. Obj. 6,3. Oc. 8. Neg. 6937.

with the latter zone is much clearer than in the ventral wall. It is made up of a line of elongated nuclei closely grouped together and indicating a clear frontier.

Summarizing the results of this preliminary examination, we can conclude that the infundibulum offers a structural plan of two layers when examined with a nuclear staining.

An examination of sagittal sections of the infundibulum this time stained with hematoxylin (after formaline-alcohol-acetic acid fixation) shows a more complete colouring of the structure, and, therefore, a more informative picture.

Ventral wall. Cells and fibres are more prominent in these — slightly overstained sections. It is now possible to distinguish three layers, owing to the more complete colouring of the whole thickness of the wall of this organ. These three layers are: an inner one formed by the cellular lining of the recessus infundibularis, about which the same things could be said as in the cresyl-violet sections. The second layer is made up of large bundles of fibres placed obliquely in relation to the axis of the infundibulum (fig. 19). Many isolated cells — already described — lie in this zone, of which only the nuclei are coloured. The main axes of these nuclei usually run parallel to the direction of the fibres.

There is no sharp borderline between these two layers; very often bundles of fibres are seen in the immediate neighbourhood of the ependymary lining of the recessus and clusters of cells, in their turn, penetrate deeply into the second layer. It is our opinion, nevertheless, that the first layer has a predominantly cellular structure, whereas the second has mainly a fibrillar one.

The fibres in the second layer belong to two categories: nerve fibres and ependyma fibres. The first ones are very thin, arranged in bundles and they run towards the processus infundibularis. The ependyma fibres are much thicker and coarser and they are directed perpendicularly to the main infundibular axis, thus crossing the nerve fibres almost at a perpendicular angle. These fibres are the direct cytoplasmic continuation of the ependyma cells of the

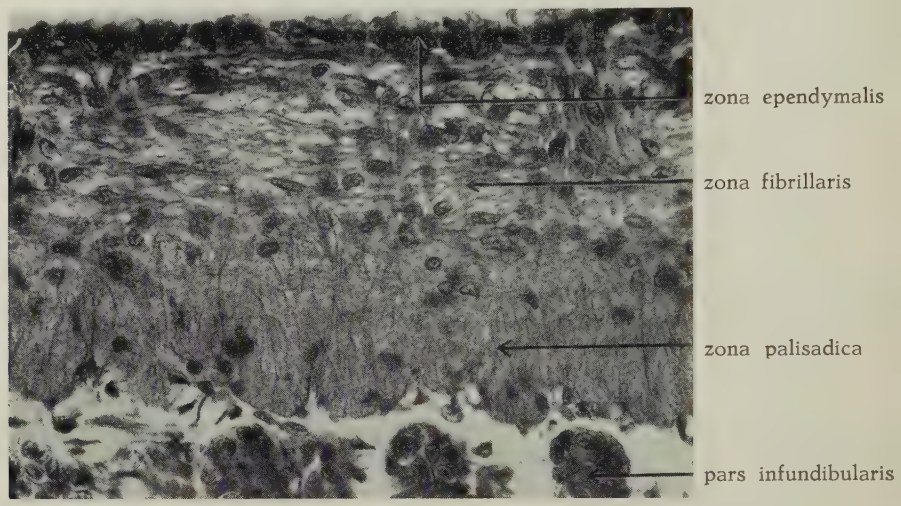


Fig. 19. Ventral wall of the infundibulum stained with hematoxylin. Obj. 4 mm. Oc. 10x. Neg. 2200.

first layer (Retzius, '94). They traverse the whole thickness of the ventral wall and at a certain point, they ramify into many fine branches, which end either around the perivascular sheath of the capillary loops or at the basal membrane of the ventral wall.

The third and more peripheral layer is already in contact with the pars infundibularis of the adenohypophysis. In our hematoxylin material, this layer appears almost devoid of cells, only a few are placed around the vessels coming from the pars infundibularis (the "mantle-plexus" of Romeis). On the other hand, it shows an extraordinary richness in fibres belonging to the distal portion and terminal arborizations of the ependyma fibres. In transversal sections, the ependyma fibres show themselves very clearly stained, above all in the lateral wall where the total course of the fibre is very often contained within the thickness of the sections. In the ventral wall, however, the middle part of the fibres (which should be contained in the second layer) is often difficult to see. We do not know if this is produced by variable staining properties of the fibres or by a somewhat irregular course of the middle part of the fibres in the ventral wall. In any case, the ependyma fibres are easily demonstrated in the third layer of any well-stained hematoxylin material. This is also the

case with azan sections.

A basal membrane separates the third layer from the pars infundibularis. Our sections seem to indicate that the terminal feet of the ependyma fibres end on the basal membrane where they suddenly stop their course (fig. 20). Sometimes the ependyma fibres may also pierce the basal membrane and penetrate into the interfollicular spaces of the pars infundibularis where they seem to merge into the connective tissue framework of this part of the adenohypophysis (figs 20a and 20b). This may also be observed in Bodian series, especially after alcohol fixation.

The basal membrane is pierced by numerous vessels which produce a number of notches on its surface. Often an ependyma fibre is attached to one of these notches.

The borderline between second and third layer is not clear in these hematoxylin sections. Nevertheless, there is a certain tendency for the cells to be situated in the frontier between the two layers where they form a loose row.

Dorsal wall. The architectural plan of the dorsal wall is revealed with great clarity in fig. 20. In the same way as in the ventral wall we also find here three layers disposed concentrically. The inner one is made of the lining of the

Fig. 20. Dorsal wall of the infundibulum. Note the terminal brush-like spreading out of the ependyma fibres in the zona palisadica. Obj. 40. Oc. 8. Neg. 8736.

recessus. Its nuclei are small and closely aggregated. One special characteristic is that all these lining cells are provided with a sort of prolongations, which affect the shape of "droplets" secreted by the lining cells of the first layer into the liquor. In general, the thickness of the cellular lining is represented by a row of two nuclei. In some sections there are accumulations of lining cells which bulge towards the lumen of the recessus apparently with a high secretory activity.

A closer examination of these problematic "droplets" reveals the following facts: they are 6-8 μ approx. in length and seem to be completely structureless; the individuality of each droplet is more conspicuous because of the presence of a very clear membrane which isolates it. Their form is more or less poliedric. This is probably caused by reciprocal pressure. They are usually disposed in one single row, but in some places, they may be piled on top of each other. It may be objected that these formations are but portions of the ependyma cells obliquely cut. I do not think so, because they are present not only in those places liable to considerable obliquity of the plane of sectioning with respect to the wall of the recessus, but in every section, even in median sagittal ones, and there is no ground for allowing for any marked degree of the obliquity of the plane of sectioning of this series.

The interpretation of these formations is certainly difficult. Collin ('47) has drawn attention to the constant destructive and degenerative processes taking place in the ependymary lining of the recessus of the cat, both adult and newborn. In his paper of '47 he says: "... Les zones irrégulières sont souvent le siège de phénomènes d'hyperplasie qui aboutissent à la formation de bourgeons saillants dans la lumière du récessus. A leur niveau, les noyaux des épendymocytes présentent de nombreuses figures de division directe et les noyaux issus de ces amitoses sont plus petits que ceux dont ils proviennent. Ces phénomènes paraissent avoir une double signification, dégénérative pour les éléments les plus superficiels, régénérative pour les éléments profonds qui tendent à se disposer de manière à reconstituer un épendyme régulier" (p. 89). According to this view the droplets are degenerated ependyma cells, and it is this view that I subscribe to. At the same time it must be admitted that the presence of droplets is not an invariable phenomenon; of our total material of cat-hypophyses amounting to 16 series they are only present in six. It seems, therefore, possible that the droplets appear only in a particular phase of the physiological cycle of the animal.

The second layer is the fibrillar one. With respect to the fibres it must be said that in general they are disposed transversally in the proximal part of the dorsal wall, becoming sagittal in more distal levels. In the proximal part it is possible to distinguish two sub-zones in the second layer; one of transversal fibres perpendicularly cut and another of more or less sagittal fibres (fig. 48). At different levels numerous cells are interspersed between the fibres. No trace of any regular arrangement of these cells was found. It is very characteristic that nerve

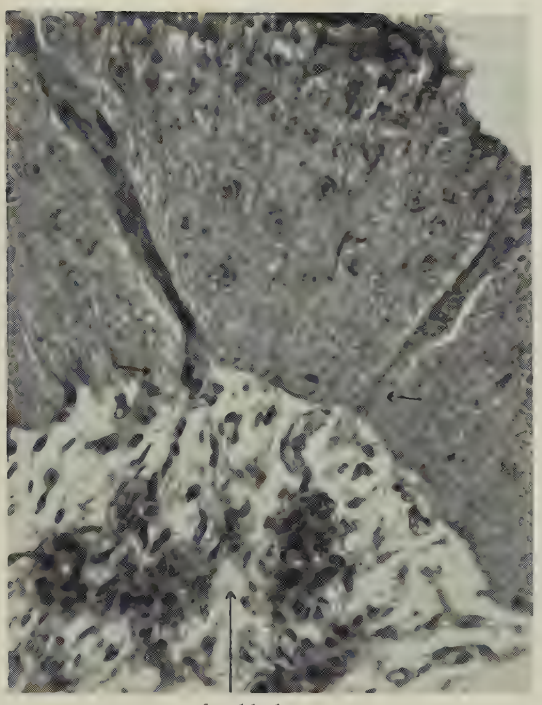


Fig. 20a. Transition zone between pars caudalis tuberis and dorsal wall of the infundibulum. Ependyma fibres are seen piercing the basal membrane and joining the connective tissue of the pars infundibularis. Obj. 40. Oc. 8. Neg. 8737.

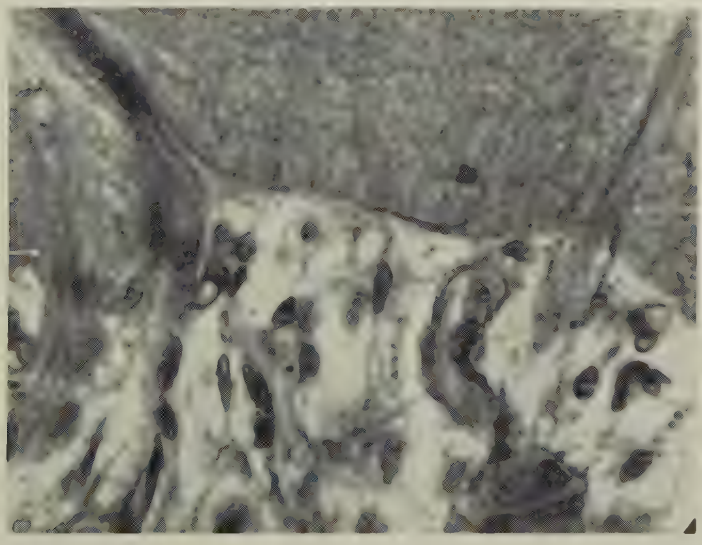


Fig. 20b. The above at high magnification. Obj. 100. Oc. 8. Neg. 8738.

cells are more frequent in the dorsal wall than in the ventral one. As a rule, these cells are more numerous the more we approach the pars caudalis tuberis, but even at levels close to the processus infundibularis they are present and are very near the ependyma. Their cytoplasm remains uncoloured.

Besides those formations which we have called "droplets", the more typical constituents of the dorsal wall are the long, thick, coarse fibres which, originating in the lining cells of the first layer, traverse the thickness of the dorsal wall to end in a delicate swelling on the basal membrane (fig. 20). They are undoubtedly ependymal fibres forming a sort of framework for the dorsal wall. In series 589, these fibres are still better stained in the dorsal than in the ventral wall. Often these fibres have thick collaterals (faintly stained in our material) which join the neighbouring fibres and this results in the formation of arches. These arches, are especially conspicuous in the processus infundibularis.

The third layer or the more peripheral one is characterized both by the scarcity of cells and by the great richness in fibres which originate outside this layer. The sections show that these thick, coarse fibres which completely traverse the thickness of the dorsal wall divide in a tuft of fine branches which insert into the basal membrane.

From the preceding description we can infer that a considerable degree of structural analogy between the ventral and dorsal wall of the infundibulum exists.

In silver-impregnated material, the picture shows a certain degree of variation, due to a number of factors: age of the animal studied, fixatives used, duration of the fixation, pH of the different solutions etc. These are but some of the many – often uncontrollable – factors influencing the silver staining. Nevertheless, after some attempts, it is not difficult to get consistently well stained Bodian series.

Ventral wall. The Bodian method also permits to distinguish three layers in the ventral wall. The first layer is constituted by the ependymary lining of the recessus to which the name "zona ependymalis" can be applied. This method stains the nuclei of these cells clearly, but the cytoplasm remains completely unstained.

The second layer stands out prominently in this material owing to the specificity of the silver-impregnation for nerve fibres. There is an intermixing of cells and fibres many of which are placed very close to the lumen. As was pointed out with regards to the hematoxylin material studied, there is no borderline between these two layers. From now on, we shall refer to the second layer as "zona fibrillaris", on account of its predominantly fibrillar constitution.

The third layer presents a somewhat peculiar structure in these silver-impregnated sections. The degree of success of the staining plays an essential role in the microscopic picture of the third layer. In poorly stained sections, it reveals itself as a rather uniform, structureless mass of a bluish-violet colour. In

well-stained sections, the third layer appears constituted by great numbers of extremely thin, pale fibres following very irregular courses. In material fixed in alcohol, the ependyma fibres are often impregnated by the silver; in formol-fixed material, on the contrary, these fibres remain completely unstained.

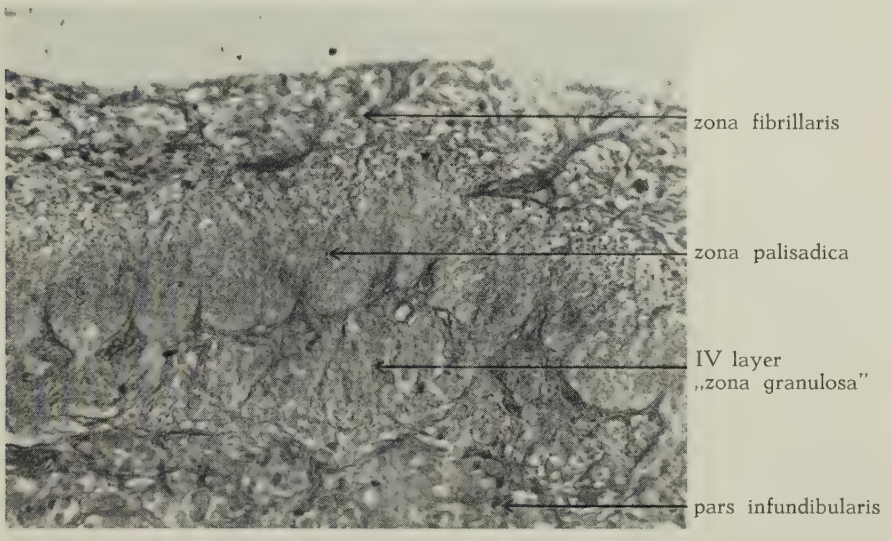


Fig. 21. Transversal section of the ventral wall (Häggqvist staining) showing the fourth layer (zona granulosa). Obj. 25. Oc. 8. Neg. 8777.

Both the scanty number of cells and the richness in vessels are confirmed in this material. This gives a special character to this layer for which we propose the provisory denomination of "zona palisadica", owing to its appearance, when the ependyma fibres are stained.

A close study of the proximal part of the ventral wall permits us to recognize even a fourth layer in the median portion of the ventral wall. This new layer attains its maximum thickness on each side of the median line and it diminishes towards the lateral wall. It does not exist either in the dorsal or in the lateral wall of the infundibulum, but only in the proximal portion of the ventral wall. It is located between the zona palisadica and the pars infundibularis being separated from the former by connective tissue septa which connect the blood vessels to each other with curved links (fig. 21). Microscopically, it does not show the same constitution as the zona palisadica, showing very few nerve fibres. The fourth layer is not always clear in Bodian sections. In material stained with the Häggqvist method, differentiation between the fourth layer and the zona palisadica is, however, easy. Following Hanström ('52) and Hagen ('55) who have been the first to identify this layer (in the dog) we call it "zona granulosa". On p. we shall give further information about the structure of this layer.

Dorsal wall. Bodian sections permit us to distinguish three layers also in the dorsal wall, at least in its middle part. It may be interesting to note that the number of nerve cells present here is substantially higher than in the ventral wall. Proximally their number increases where they form the nucleus infundibularis (pars posterior).

The zona fibrillaris is by far the thickest constituent of the dorsal wall. There is no limit with the zona ependymalis; cells and fibres mingle freely throughout the dorsal wall. The nerve fibres are disposed very irregularly, above all in the proximal part of it where they form a tangled mess. Distally, on the contrary, they are arranged much more regularly, following a sagittal direction which allows us to trace them further. In the proximal part of the dorsal wall they are almost perpendicular to the plane of sectioning.

Contrary to current views (Nowakowski, '51), the zona palisadica is also present in the dorsal wall, as can be seen in fig. 22. It is interesting to note that this zone is absent in the proximal part of the dorsal wall, i.e., it does not begin immediately after the disappearance of the glial lining of the pars caudalis

Fig. 22. Gomori-stained section (from the collection of the Max-Planck Institut of Giessen) showing the existence of a well-developed zona palisadica in the dorsal wall. 70x.

tuberis, but further distally. Frontal sections confirm this conclusion; the zona palisadica is not present in the proximal part of the dorsal wall (fig. 23) but more distally in the same series, it is clearly represented (fig. 22).

The zona palisadica of the dorsal wall is less thick than its homologue in the ventral wall. Practically no cells are placed here. Under high magnification it seems to be constituted by very thin filaments disposed perpendicularly to the axis of the infundibulum. Now and then, some fragment of a longitudinal fibre is found. Blood vessels coming from the pars infundibularis are also present.

In the course of this description, we have tried to make clear that the dorsal

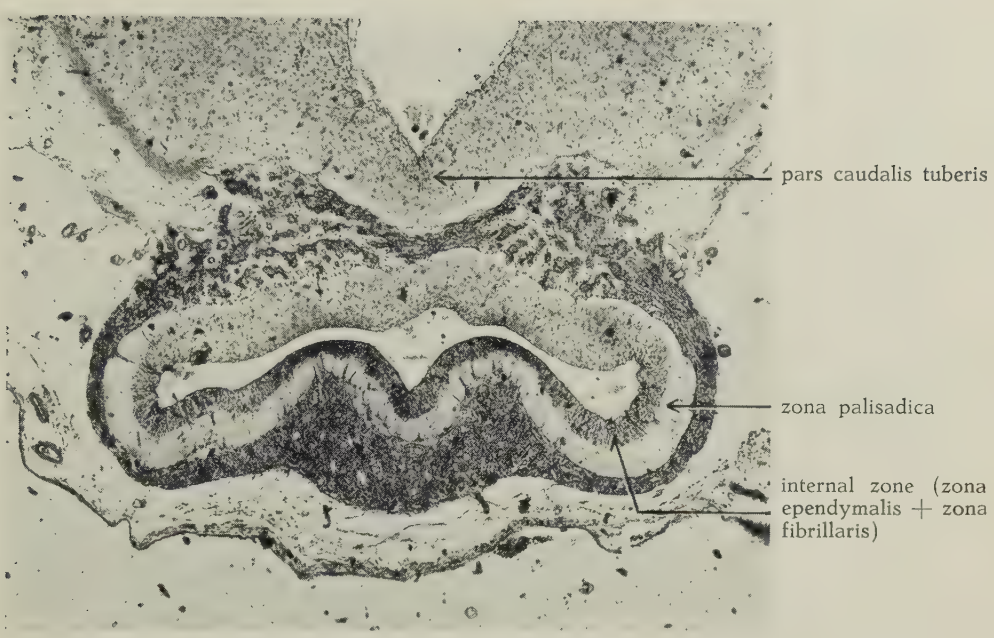


Fig. 23. Gomori-stained section (from the Max-Planck Institut of Giessen) showing a well-developed zona palisadica in the ventral and lateral wall, but not in the dorsal wall. 45x.

and ventral wall of the infundibulum are built according to the same structural plan. It remains to be seen now if the lateral part also shows the same constitution. Frontal sections are most suitable for this purpose. A glance at them is enough to show the three layered structural plan again. The similarity is so complete that we shall not describe it to avoid repetitions. It is worth remarking, however, that the zona palisadica is very well-developed, and even surpasses the same zone of the ventral wall in thickness, especially in distal levels (fig. 23).

In his important paper on the infundibulum of the cat, Nowakowski ('51) describes the ventral wall of the infundibulum as composed of two layers. These are the "zona interna" (comprising our zona ependymalis and our zona fibrillaris) and the "zona externa" (corresponding to our zona palisadica). On the other hand, he states that such a distinction is not feasible in the dorsal wall which, according to him, is constituted by the "zona interna" only. I cannot agree with him on this last point: the figures speak for themselves. The zona palisadica in the dorsal wall is indeed, less developed than in the ventral but not in such a degree as to be negligible.

The adenohypophyseal partner of the zona palisadica is the pars infundibularis. There seems to exist a certain correlation between these two structures, because as soon as the infundibulum is lined by the "nasale Umschlagzone" (Romeis, '40) or the pars intermedia, the zona palisadica disappears.

If we now try to summarize the results of our observations about the histo-

logical structure of the cat-infundibulum, we arrive at the following conclusions:

1. The walls of the infundibulum are built according to the same plan of structure (with the exception of some minor changes, for example the inexistence of the IV layer – "zona granulosa" – in the dorsal wall).

2. This structural plan consists of three layers concentrically disposed possessing a marked individuality. These are: 1. The zona ependymalis. 2. The zona fibrillaris. 3. The zona palisadica.

* * *

The structure of the region of the infundibulum midway between its proximal and distal ends is in strict accordance with the above description. It is necessary to determine now if this structural plan also holds good for the whole length of this part of the neurohypophysis. This question is very intimately related with another important one: the problem of the microscopic limits of the infundibulum. In order to establish these limits as accurately as possible, a careful examination of the structure of the entrance area and of the transition area with the processus infundibularis is necessary.

A. STRUCTURE OF THE ENTRANCE AREA

1. *Ventral and lateral lips.* Nowakowski ('51) has drawn attention to the structural changes occurring in the transition zone tuber cinereum-infundibulum. He pointed out that in this zone, the number of nerve cells greatly increases – in such a way that it is possible to speak of a "wedge of ganglion cells penetrating into the neurohypophysis". These cells belong to the n. infundibularis. The wedge of nerve cells thins out quickly in the direction of the processus infundibularis so that in by far the greater part of the infundibulum only scattered nerve cells are found. In the dorsal wall the nerve cells reach more distal levels than in the ventral one.

The wedge of nerve cells of the entrance area is interposed between the zona ependymalis and the zona fibrillaris separating the latter and the corresponding zona palisadica from the lumen of the recessus infundibularis. Nevertheless, these cells do not belong to the infundibulum; they belong to the n. infundibularis and this is a part of the tuber cinereum. That means that the transition area of the infundibulum to the tuber is certainly not clear cut; over a certain extension the tuber overlaps the infundibulum and vice versa. This is true for the whole extension of the entrance area.

If we take the sulcus tuberis infundibularis together with the termination of the lining of the pars infundibularis as the proximal limit of the infundibulum, then the typical three layered plan of structure of the infundibulum is altered because of the above mentioned overlapping of tuber elements. In this proximal part the wall is formed only by two infundibular components (this is not completely exact; see following chapter), the zona fibrillaris and the zona palisadica, because the nerve cell conglomerates situated here, belong to the tuber cine-

reum. This proximal region of the infundibulum is called "radix infundibuli" (Nowakowski, '51).

Summarizing what we have said, it is clear that large groups of nerve cells belonging to the n. infundibularis wedge themselves between the zona ependymalis and the zona fibrillaris over a certain extension beyond which the number of these cells is not significant any more. The structure of the proximal region of the infundibulum is broken, being now actually constituted by four layers (ependymalis, wedge of nerve cells, fibrillaris and palisadica), one of which belongs to the tuber cinereum.

2. Dorsal lip. In the dorsal lip and its corresponding wall the situation is very similar. The dorsal wall is the continuation of the pars caudalis tuberis which in turn, forms the bottom of the recessus mamillaris. The pars caudalis tuberis also has an ependymary lining continuous with the ependyma of the dorsal wall. Caudally, it is partly lined by the pars infundibularis of the adenohypophysis, forming the roof of the very deep sulcus infundibularis. In cresyl-violet sections, numerous nerve cells belonging to the n. infundibularis are seen. They are regularly disposed in layers occupying almost the whole thickness of the region. Particularly interesting is the fact that these nerve cells also lie in the most caudal part of the region, not far from the lining of the pars infundibularis (fig. 18). In Bodian material, a fibrillar system appears very near the basal side of the pars caudalis tuberis of which the fibres are continuous with the fibres of the dorsal wall (fig. 47). If we examine the transition zone of the pars caudalis tuberis and the dorsal wall, we see three important changes. These are: 1. The nerve cells of the nucleus infundibularis retire from the proximity of the pars infundibularis lining, i.e., they withdraw to more central zones (fig. 18). 2. They greatly diminish in number. 3. The glial lining of the base of the diencephalon disappears. The transition zone between pars caudalis tuberis and dorsal wall is again constituted by four layers, or rather, by three because the zona palisadica is not clear in this proximal level (the same is also the case in the ventral and lateral lip). These layers are: the zona ependymalis, the wedge of n. infundibularis nerve cells and the zona fibrillaris. *The analogy with the situation found in the ventral and lateral wall is complete.*

The changes listed above coincide to a certain degree, so that the transition zone between tuber and dorsal wall is of reasonably short extension. In this transition zone we find that its inferior part consists of infundibulum, at least of the zona fibrillaris and perhaps traces of the zona palisadica, whereas the n. infundibularis tuberis forms the superior part of it.

B. STRUCTURE OF THE TRANSITION BETWEEN INFUNDIBULUM AND NEURAL LOBE

In chapter II we have made an almost macroscopic distinction between these two parts of the cat neurohypophysis, based on the thickness of he wall. We have

said thus that infundibulum is that part of which the walls have more or less the same thickness, and the neural lobe is that part of the neurohypophysis of which the walls are strongly thickened. The study just made of the histology of the infundibulum enables us to distinguish these two parts more accurately. Again sagittal and frontal sections are most adequate for this purpose.

A very careful study of the dorsal wall in our sagittal series results in the somewhat unexpected conclusion that it is impossible to find anything which could indicate a borderline between the dorsal wall of the infundibulum and the dorsal part of the neural lobe. The latter, at least in the median sagittal plane, is just the continuation of the dorsal wall of the infundibulum showing

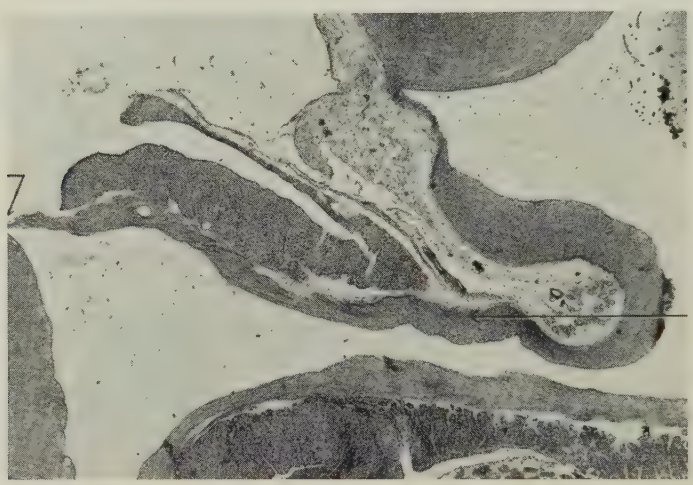


Fig. 24. Median sagittal section of the neurohypophysis of the cat. The roof of the neural lobe consists of the distal prolongation of the internal zone of the infundibulum. Bodian stain. Obj. 16 mm. Neg. 8744.

exactly the same histological constitution. The roof of the central cavity of the processus infundibularis is formed by an ependymary lining (zona ependymalis) and by bundles of nerve fibres of which the majority pursue a strictly sagittal direction whereas others, also forming bundles, diverge to go to other areas, probably the well-developed lateral parts of the neural lobe. But the typical components of the neural lobe tissue (Herring's "light and dark areas"; "Verdichtungszonen und Zwischenstreifens" of Romeis) are lacking in this roof. The dorsal wall of the neural lobe is formed exclusively by infundibular elements, the zona ependymalis and the zona fibrillaris. This means that what seems to be the dorsal wall of the neural lobe is actually constituted by the "central zone" of the infundibulum. ("central zone" = zona ependymalis and zona fibrillaris). The zona palisadica in the dorsal wall of the neural lobe is not present, thus confirming the rule that where the pars intermedia lines the neurohypophysis, the zona palisadica is absent. The conclusion is that the dorsal wall

of the infundibulum (or at least its central zone) reaches as far as the dorsal (aboral) pole of the neurohypophysis (fig. 24).

An examination of the ventral wall yields the following facts: shortly before the terminal swelling of the neurohypophysis (the neural lobe) begins, the ventral wall of the infundibulum — lined by the "nasale Umschlagzone" and the pars intermedia — is constituted by the zona ependymalis and the zona fibrillaris, i.e., by the central zone. Shortly afterwards the wall thickens considerably, owing to the appearance of the tissue proper of the neural lobe (Herring's light and dark areas). It must be noted that this tissue is not in contact with the lumen of the recessus, on the contrary, it is always separated from it by a thin layer which preserves its infundibular (central zone) character, that is to say, by a layer constituted by an ependyma and by nerve fibres running parallel to each other and grouped in bundles. Ependyma fibres are also present, running perpendicular to the former and eventually attaching themselves to the perivascular connective sheath of the infundibular capillary loops which are also present in this area (see chapter VI). The ependyma fibres are often seen anastomosing with the neighbouring ones and forming arches.

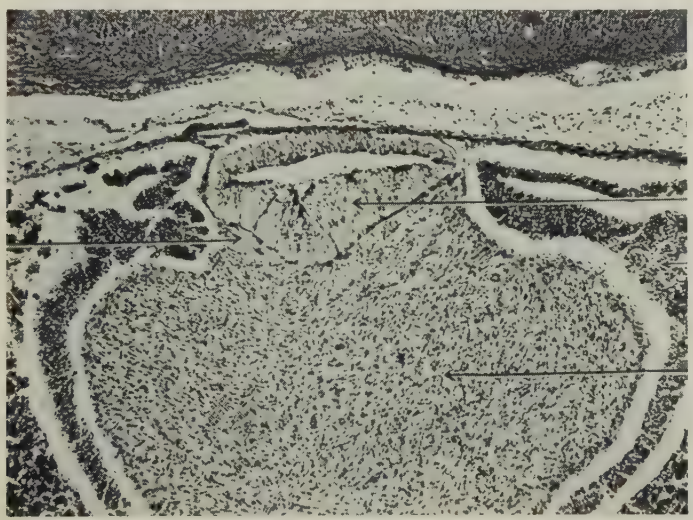


Fig. 25. Transversal section of the neural lobe. Note the „mantle-plexus" separating the central from the peripheral zones of the neural lobe. Obj. 6,3. Oc. 8. Neg. 6929.

We see thus that the lumen of the recessus infundibularis is limited over its whole extension by a layer constituted by infundibular tissue (zona ependimalis and the zona fibrillaris). This happens not only in proximal levels of the neurohypophysis but also in the most distal part of it (neural lobe). The tissue characteristic of the neural lobe has the signification of a "peripheral zone" (zona externa). Nowhere does it reach the lumen of the recessus. This means that in the processus infundibularis itself it is also possible to distinguish two

zones: one internal, forming the immediate wall of the lumen, representing the "central zone" of the infundibulum, and another peripheral, constituted by the tissue characteristic of the neural lobe, which represents "external zone".

The disposition of the ependyma fibres and the vascular arrangement of the blood vessels strongly support this conception.

The division of the processus infundibularis into two zones is substantiated by our observations in material belonging to young cats (fig. 25). It can be seen how a row of cells representing intervascular connective tissue neatly separates the prolongation of the internal zone of the infundibulum from the peripheral zone of the neural lobe (Herring's light and dark areas). The zona interna of the infundibulum does not lose its individuality even in the very mass of the processus infundibularis, of which it forms the central zone. In more distal sections of the same series, it can be seen that the line formed by the connective tissue is broken by the numerous nerve fibres which spread fan-like to reach the light areas. The disruption of this line is never so complete as to disappear without leaving rests. (fig. 26).

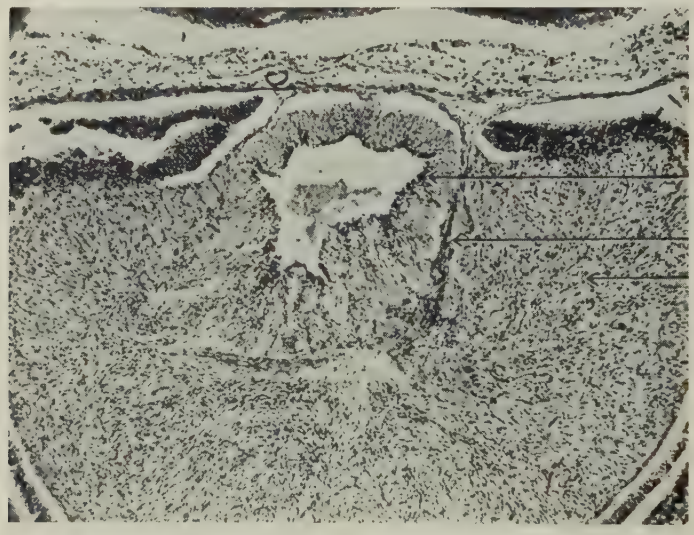


Fig. 26. Transversal section of the neural lobe at more distal level. The barrier between central and peripheral zones of the neural lobe is partly broken. Obj. 6,3. Oc. 8. Neg. 6930.

II. THE NERVOUS COMPONENTS OF THE NEUROHYPOPHYSIS OF THE CAT

The above mentioned data on the structure of the cat-neurohypophysis allow us to suggest a new division of it. We think that it is essential to distinguish between the central zone (comprising the zona ependymalis and the zona fibrillaris) and a peripheral zone (comprising the zona palisadica in the proximal hypophysis and the light and dark areas of the neural lobe). The central

zone forms the wall of the recessus infundibularis over the whole extension, except for the transition area between infundibulum and tuber cinereum (wedge of the n. infudibularis nerve cells). Its histological structure is uniform, i.e., it is constituted by an ependyma, by parallel-running bundles of nerve fibres, by numerous cells (pituicytes and neuroglia) and by ependyma fibres often anastomosing and forming arches. The structure of the central zone is always the same at any level of the neurohypophysis.

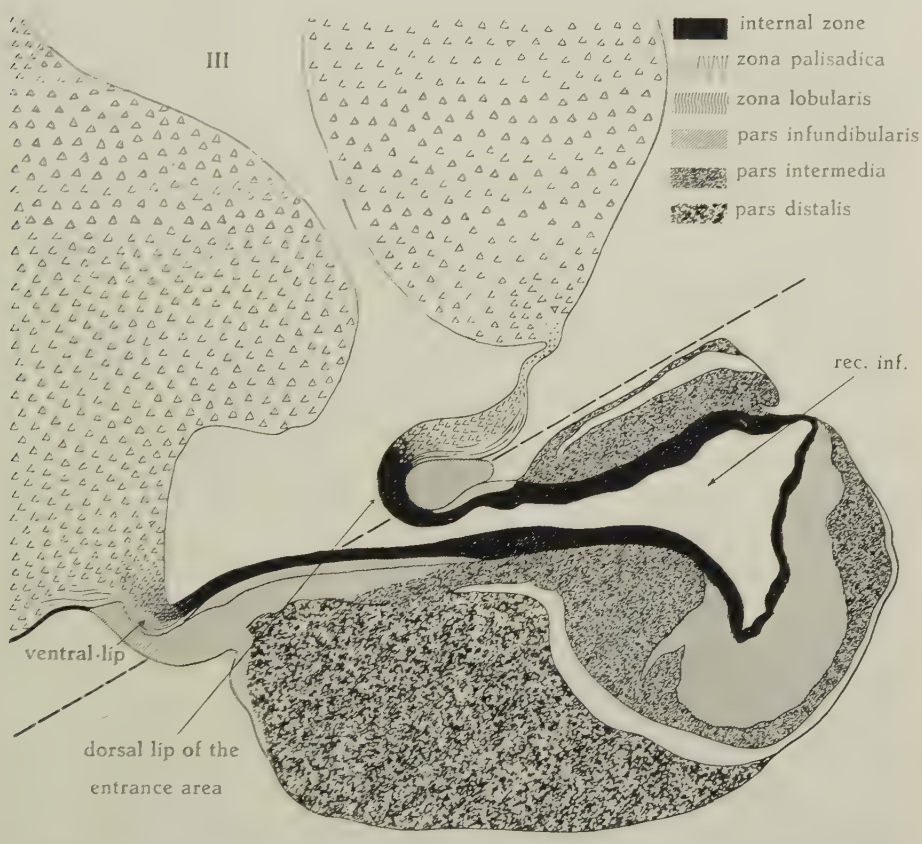


Fig. 27. Diagrammatic representation of a median sagittal section of the hypophysis of the cat. Note the zona palisadica in the dorsal wall of the infundibulum.

The structure of the peripheral zone, on the contrary, shows a considerable degree of variation according to the place considered. In the proximal portion of the neurohypophysis we have called it the zona palisadica, and is not present in the dorsal wall. (fig. 23). In the middle portion of the neurohypophysis, the situation is inversed since the zona palisadica is present in the dorsal wall but not in the ventral one. (fig. 22). In the distal portion of the neurohypophysis, the peripheral zone has no longer the same structure as the zona palisadica

(although they are not essentially different). In fact it is no longer zona palisadica but Herrings's light and dark areas. Contrary to the continuity and uniformity of structure characteristic of the central zone, the peripheral one is neither continuous nor uniform.

We have represented our ideas on the histological constitution of the cat-neurohypophysis in fig. 27. The central zone of the infundibulum is represented in black. This zone comprises our zona ependymalis and zona fibrillaris. At a glance we notice that this zone forms the core of the neurohypophysis, forming at all levels the wall of the lumen. In the median sagittal plane it also forms the dorsal wall of the neural lobe which at this level, lacks its peripheral zone. The uniform black colour suggests the uniformity of the structure found at all levels.

The external (peripheral) zone of the neurohypophysis is drawn with different dotted lines owing to its different structure acording to the level considered. The peripheral zone of the proximal neurohypophysis is the zona palisadica. In fig. 27 it is represented by dotted lines. It can be observed that the zona palisadica does not exist at the insertion area of the infundibulum in the tuber cinereum (entrance area).

In the terminal dilatation of the neurohypophysis (neural lobe) two layers can again be distinguished. The internal one is the direct continuation of the internal zone of the infundibulum. The external represents that particular tissue of the neural lobe which is constituted by light and dark areas. The structure of the latter is not essentially different from that of the zona palisadica, but there are differences enough to be distinguished. The peripheral zone of the neural lobe is given as a undulating dotted line in the scheme.

In my opinion, this division of the neurohypophysis into two parts, the central zone (of uniform structure) and the peripheral zone (not continuous and of different structure according to the level considered) is both simple and in strict agreement with the histology of the whole organ. From the developmental point of view, the peripheral zone represents a territory appearing late in the development. It is well known that the processus infundibularis appears for the first time in cat-embryos of about 40-50 mm. crown-rump length, but the primitive infundibular diverticulum is present already in embryos of 6 mm. *The neural lobe is formed by the progressive thickening and differentiation of the most distal part of the ventral wall of the primitive infundibular diverticulum. Its dorsal wall does not take part in forming the neural lobe.*

The central zone of the neurohypophysis might be considered as representing the wall of the primitive infundibular diverticulum. It is true that it is not possible to consider the peripheral zone of the neural lobe separated from the central zone. Both structures are integrated and form a unity and the one cannot exist without the other, but this does not prevent us from believing that the peripheral zone of the adult neurohypophysis is just a regional differentiation of the primitive infundibular wall, which appears more or less late in the deve-

determining factors of the formation of the external zone of the neurohypophysis; it is possible that phenomena of interactive differentiation play a rôle in the formation of the external zone, as they do in the pars intermedia. The entrance of numerous axons originating in the hypothalamic nuclei may also play a rôle in the thickening of the ventral wall. It is also likely that the blood vessels exert an important influence on the development of the external zone of the neurohypophysis. This zone which may be considered as the place of termination of part of the hypothalamic nerve fibres, is characterized – with the exception of the lateral wall of the infundibulum – by its great richness in vessels. Little information is available on the stage in the development in which the blood vessels penetrate into the neurohypophysis, but there are some grounds for assuming that this is a late one (according to Brahms, '32, the vessels enter the neural lobe in embryos of 19 mm). A great deal of more work could be done to clarify these obscure points.

The ideas which we have just put forward lead us to the following conclusions:

1). *Two structurally different regions may be distinguished in the neurohypophysis. These are: a) the internal zone. b) the peripheral zone.*

2). *With the exception of the entrance area, the internal zone limits the cavity of the recessus infundibularis over the whole extension. Its structure is the same at all levels of the neurohypophysis, being constituted of two layers, the zona ependymalis and the zona fibrillaris.*

3). *The peripheral zone is not a continuous layer of tissue because it is interrupted at three different places. These places are: a) the entrance area. b) the middle part of the ventral wall. c) the dorsal wall of the neural lobe in the median sagittal plane. The structure of the peripheral zone shows important local differences which allows a distinction between the zona palisadica and the external zone of the neural lobe which might be called "zona lobularis", in attention to its peculiar lobular organization. The peripheral zone may be considered as a particular neurohypophyseal area which appears late in the development.*

4). *The transition area between the infundibulum and the tuber cinereum shows a considerable degree of overlapping of these two territories. In spite of this, the sulcus tuberis infundibularis may be taken as the landmark indicating the proximal limit of the neurohypophysis. This limit coincides with reasonable accuracy with the disappearance of the glia externa lining of the base of the brain (Nowakowski, '51).*

CHAPTER V

THE TOPOGRAPHY OF THE HYPOTHALAMIC INNERVATION OF THE NEUROHYPOPHYSIS

The main purpose of this thesis is indeed, to make a topographic study of the situation and the site of termination of the hypothalamic nerve fibres which supply the neurohypophysis. These fibres originate in different, paired nuclei, such as the nucleus supraopticus, paraventricularis etc. Since the neurohypophysis seems to be a single organ macroscopically, we can ask ourselves if, e.g., the fibres coming from regions situated in the right side of the hypothalamus, course and distribute themselves in the right half of the neurohypophysis or, on the contrary, by means of crossings and/or deviations, if they pass the median line to end in the left half of the neurohypophysis. In other words, we shall try to find – on strictly morphological grounds – a correlation between the topographical position of the nerve fibres both in the infundibulum and in the neural lobe. To achieve this aim, we have to establish a topographical division which allows us to distinguish a number of different regions in the neurohypophysis. This division must be suitable for any level of this organ. Once this topographical division has been established, we must trace the nerve fibres as accurately as possible, in order to see if a particular fibre bundle preserves its position along its course or not. We hope to be able to correlate the position of the fibre bundles at proximal and distal levels of the neurohypophysis and to secure some information concerning the topography of the hypothalamic nerve supply in this way.

There are few references to this question (Laruelle 1934; Fisher, Ingram and Ranson 1935, Nowakowski 1951, Spatz 1958). It is generally believed that the nerve fibres in the dorsal wall have a smaller diameter than those of the ventral one. It is also claimed that these differences in diameter are related to the distance of the nuclei of origin of the fibres to the neurohypophysis. It has, moreover, been suggested that these thin fibres enter the neurohypophysis through the dorsal wall from which they pass into the ventral wall to innervate the "capillary loops" of the zona palisadica. These statements have never been demonstrated.

A second question to which considerable attention has been paid is that of

the histological structure of the zona palisadica. A great deal of work has been done in the last years to clarify this point, which the majority of scientists have considered highly important. It is generally accepted — on insufficient histological evidence — that an extremely thin plexus of nerve fibres is present in the zona palisadica; this plexus innervates the capillary loops (Green and Harris '46; Wingstrand '51; Nowakowski '51; Benoit et Assenmacher '55). According to these authors, the functional importance of this innervation of the "capillary loops" is great for the hypothalamic control of the hypophysis.

The study of the general morphology of the infundibulum of the cat made in chapter II, helps to establish a simple and reliable topographical division of the neurohypophysis. In this species, the recessus infundibularis extends itself as far as the central part of the neural lobe. This circumstance provides a natural landmark which enables us to distinguish several regions in the wall. The continual presence of the recessus is a further safeguard against possible errors in the delimitation of the regions. Furthermore, the flattening of the infundibulum makes the distinction between the different parts much easier than would be the case, if the infundibulum were circular in a transversal section.

We have said that the infundibulum shows an ellipsoid form in a cross section. An approx. horizontal plane following the main axis of the ellipse divides the infundibulum into two halves, one inferior and the other superior. These two halves are approx. symmetrical. They are called ventral (caudal) and dorsal (cranial) walls, to which numerous references have appeared in preceding pages. A second plane perpendicular to the first, divides the infundibulum in a right and a left half, again more or less symmetrical. The four regions into which the infundibulum is divided, are almost of equal size, with the exception of the most proximal part of the infundibulum, where the dorsal wall is not yet completely formed.

Exactly the same division can be used in the neural lobe. In this part, owing to the considerable increase in thickness of the ventral wall of the primitive infundibular diverticulum, the size of the ventral (caudal) region is much larger than that of the dorsal (cranial) one. This is due to the fact that in the adult cat, the dorsal wall preserves the primitive infundibular character, typical of the embryonic stage up to 50 mm crown-rump length, whereas the ventral wall of the primitive infundibular diverticulum thickens considerably to give rise to the "peripheral zone" of the neural lobe, i.e., to that characteristic tissue in which light and dark areas can be distinguished.

These differences in structural differentiation are responsible for the fact that our transversal sections show the neural lobe as consisting of strongly asymmetrical ventral and dorsal halves.

It is clear that the whole neurohypophysis can be divided into four quadrants, two dorsal and two ventral. In each of these quadrants we can observe fibre bundles placed near the median line and bundles situated laterally. Our

task is to study the fibre systems and to localize and trace them from proximal towards distal, at the same time recording the possible changes in position which they may undergo along their course.

This description is based on the study of 16 series cut in four directions namely, sagittal, transversal, horizontal and parallel to the infundibular axis. Further technical data on the material used can be found in the following table:

SAGITTAL SERIES.	Ser. 589.	10u.	Bodian/H.E.	Adult.
	Ser. 226.	10u.	Bodian.	Adult.
	Ser. 257.	10u.	Bodian.	New-born.
	Ser. 1567.	15u.	Bodian/cres. viol.	Adult.
TRANSVERSAL SERIES.	Ser. 213,	10u.	Bodian/Tol. blue.	Adult.
	Ser. 1370.	8u.	Bodian/Azan.	Adult.
	Ser. 1140.	15u.	Bodian.	Adult.
	Ser. 1366.	8u.	Häggqvist.	Adult.
	Ser. 1367.	8u.	Häggqvist.	Adult.
	Ser. 1604.	15u.	Bodian.	3 weeks.
	Ser. 1601.	15u.	Bodian.	3 weeks.
HORIZONTAL SERIES.	Ser. 562.	10u.	Bodian/Tol. blue.	Adult.
	Ser. 465.	10u.	Bodian/Azan.	Adult.
	Ser. 560.	10u.	Bodian/Tol. blue.	Adult.
SERIES PARALLEL TO THE INF. AXIS.	Ser. 1492.	12u.	Bodian.	Adult.
	Ser. 1581.	25u.	Cajal.	Adult.

The greater part of our observations on the topography of the nerve fibres is based on Bodian material, which had been fixed either in 96% alcohol or in 10% formaline. The fixation was made by direct perfusion of the fixative through the aorta of the anesthetized animal. Formol fixation gives better results than alcohol fixation. Long periods of fixation with frequent changes of the fixing fluid improve the results of the Bodian technique. Adult animals are to be preferred because of the better results.

Series 1576, 1370, 1140, 1604 and 1942 were stained according to Bodian's double impregnation method, i.e., the slides – after reduction subsequent to the first protargol bath were carefully washed several times in distilled water and placed for the second time in a new bath of protargol with copper in the incubator at 37C. After this second period of 24h in the protargol bath, they were reduced for the second time in the hydrochinon-sulphite bath for 10 min. The subsequent steps were made according to the original formula. Gold toning was considered essential. The Roques brand of protargol has been used throughout. Buffering of the protargol bath at the optimal pH for nerve fibres avoids staining of the connective tissue fibres and of neuroglia.

* * *

In the following pages, the course and topography of the fibres of the tractus hypothalamo-hypophyseus will be described. We deal mainly with three questions; 1., The detailed topography of the hypothalamic fibres running together into the entrance area of the infundibulum. 2., The topography of the fibres inside the infundibulum. 3., The areas of termination of these fibres.

I. THE TOPOGRAPHY OF THE HYPOTHALAMIC FIBRES IN THE ENTRANCE AREA

A) *Ventral lip.* Shortly before their entrance in the ventral lip of the entrance area, the nerve fibres are situated more or less horizontally in the pars oralis tuberis where they occupy a very superficial position. At more rostral levels in this zone, they are interwoven among fibres of Ganser and Gudden commissures. As we proceed backwards, both commissures diminish progressively and the base of the diencephalon thins out to become ventral lip and still further, ventral wall.

Microscopically, two sub-zones can be observed in the ventral lip of the entrance area. In the superficial one – in contact with the beginning of the lining of the pars infundibularis – we find the hypophyseal fibre bundles placed more or less horizontally. The internal sub-zone, forming the cleft-like bottom of the third ventricle, is occupied by the cells of the nucleus infundibularis. This is what we have called the "wedge of n. inf. nerve cells" which, separating the zona fibrillaris from the zona ependymalis forms the "radix infundibuli".

At this level, we can distinguish three fibre tracts which converge in the ventral lip of the entrance area (fig. 28). These are: 1., The periventricular system of fibres, formed by numerous fine fibres closely enveloping the slit-like cavity of the third ventricle. These fibres descend parallel to the wall of the ventricle towards the ventral lip. Once they arrive at the n. infundibularis wedge zone, their further course is difficult to determine. The origin of these fibres can at least in part be traced back to the nucleus paraventricularis, n. hypothalamicus ventromedialis (nucleus principalis of Cajal) and n. infundibularis (nucleus arcuatus).

2.,The system of the perifornical fibres. This group, placed more laterally, comes from an area which surrounds the fornix. The main part of these fibres loop over the cranial border of the fornix and, following a curve of lateral convexity, bifurcate into two main bundles: one of which penetrates into the neurohypophysis through the ventral lip and the other seems to end in the pars posterior of the nucleus supraopticus (fig. 28). The origin of these fibres is difficult to ascertain but it seems fairly probable that both the n. paraventricularis and the n. perifornicalis contribute to the formation of this bundle. We suggest that collaterals from the fornix itself may also contribute to the formation of this bundle.

3., The system of the supraoptical fibres. The n. supraopticus of the cat is

constituted mainly by two groups of neurons. The larger group, has the form of a comma, placed above the chiasm and extending backwards over the optic tracts over a certain distance. Its most anterior part is in contact with the recessus suprachiasmaticus. The second and smaller group is placed in the pars oralis tuberis, between the chiasm and the ventral lip of the entrance area. The axons of the neurons of the first group are an important component of the hypothalamo-hypophyseal bundle. These fibres, situated very laterally, run more or less parallel to the superior border of the chiasm, approaching the mid-line and concentrate in the ventral lip. They mingle partially with the fibres of the second system (system of the perifornical fibres).

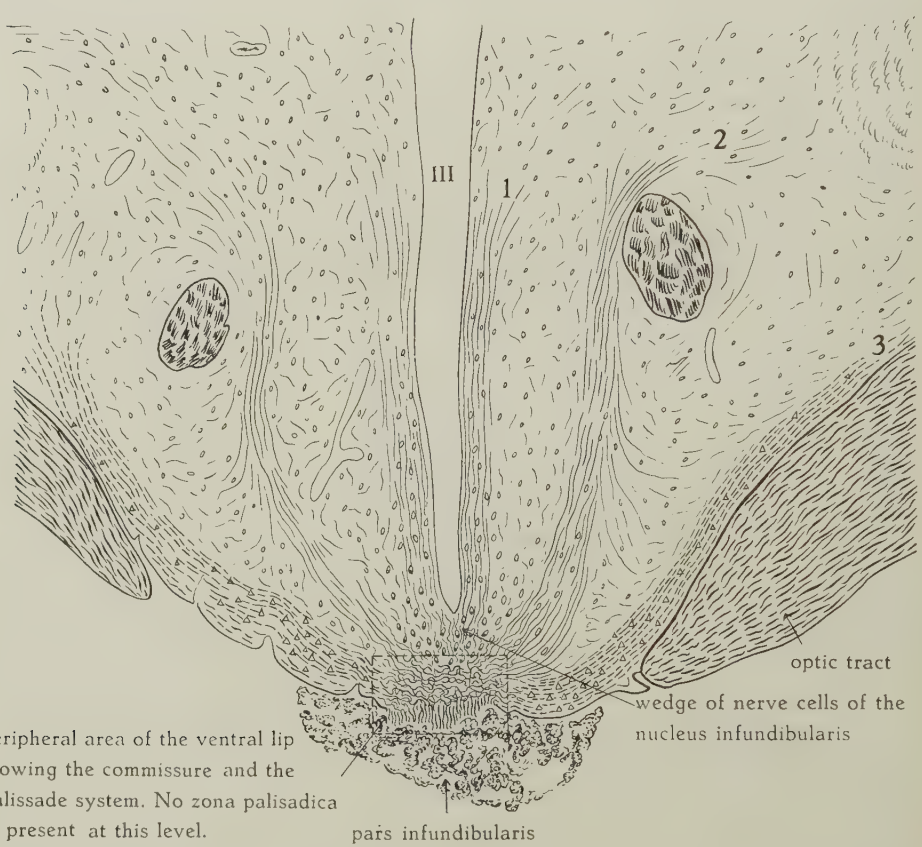

III
1
2
3
optic tract
wedge of nerve cells of the nucleus infundibularis
Peripheral area of the ventral lip showing the commissure and the palissade system. No zona palisadica is present at this level.
pars infundibularis

Fig. 28. Drawing from a frontal section showing the arrangement of the nerve fibres in the tuber cinereum at a level corresponding with section A of fig. 9. 1 = periventricular tract. 2 = perifornical tract. 3 = supraoptic tract.

The pars posterior of the nucleus supraopticus is situated behind the chiasm in the region known as the pars oralis tuberis, very close to the surface. The cells of this group are large, with two or three long dendrites. Our attempts at tracing the axons of these cells into the ventral lip have been only partly succes-

ful. After careful examination we got the impression that many of these axons (or dendrites?) are directed upwards and point towards the n. paraventricularis. In doing so, they cross the lateral fibre system constituted by the most posterior part of Ganser and Gudden commissures and second and third components of the hypothalamo-hypophyseal tract.

The peripheral zone of the ventral lip is formed exclusively by nerve fibres and neuroglia cells. No nerve cells are present here. The peripheral zone can be subdivided into two regions, one of which has an intermediate position and the other, right under the surface, is in contact with the pars infundibularis (fig. 29). In the intermediate sub-zone the fibres are disposed more or less transversally. Part of them cross the mid-line. It is, therefore, possible to speak of a partial decussation of the nerve fibres in the ventral lip of the entrance area (fig. 30).

The system of perifornical fibres must be held responsible, at least partially, for the formation of these commissural fibres.

The most peripheral sub-zone is formed by a system of fibres disposed palisade-like. The fibres are visible in these sections over very short distances. They run perpendicular to the commissural system and are placed between the commissural system and the pars infundibularis of the adenohypophysis. This is just the place where the zona palisadica is expected, but to our surprise no zona palisadica is present in the ventral lip (see chapter VI).

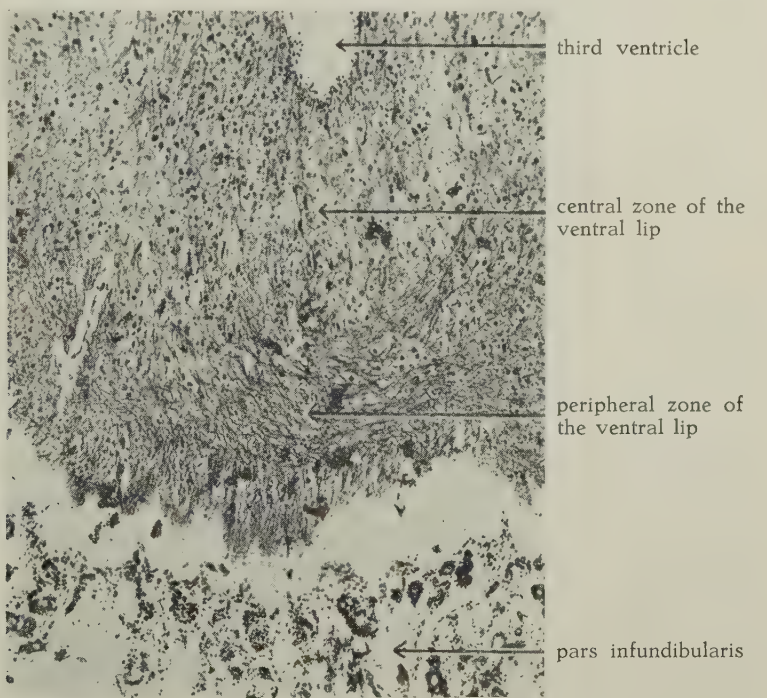


Fig. 29. Ventral lip of the entrance area. Obj. 6,3. Oc. 8. Neg. 8629.

Attempts at tracing the palisade-like system of fibres have yielded the following information: in fig. 28 a small fibre tract can be seen coming from the n. infundibularis wedge zone and after crossing the commissural system it reaches the palisade system. A second source of these fibres is either the collaterals of the transversal system placed higher (periformical fibres) or periformical fibres themselves which after running together with the commissural system of the ventral lip, abandon it to reach the neurohypophysis.

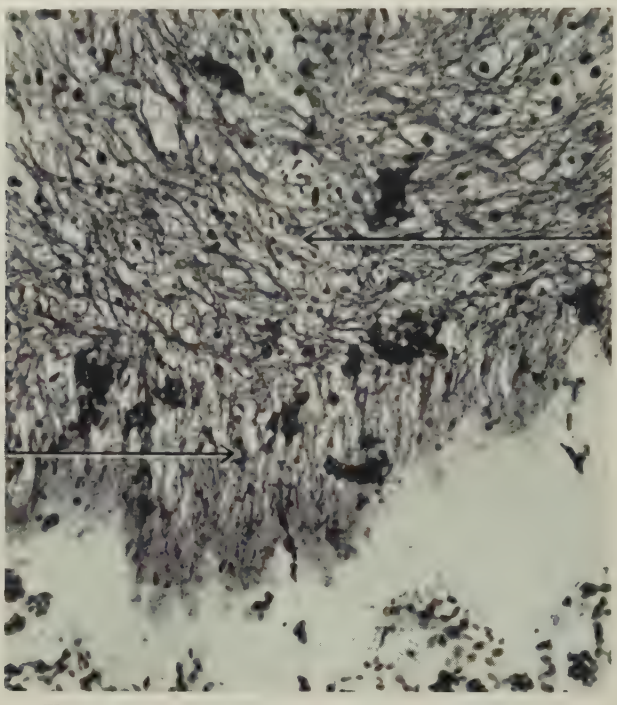


Fig. 30. The above at high magnification. Obj. 16. Oc. 8. Neg. 8751.

The periformical system is very clear in series 1140, where after turning around the medial side of the fornix, it is divided into three main components. These are: a) the most medial of them which joins the periventricular system and descends towards the ventral lip. b) the middle one, which descends also and converges towards the medial plane, where it fuses with fibre bundles originating from the supraoptic system. From the confluence of these fibres a sort of commissural group of fibres results. c) the lateral one which seems to get lost partly among the cells of the n. supraopticus and partly among the cells of the lateral hypothalamic area. The b) component corresponds probably with the so-called "fasciculus hypothalamicus" of Krieg or the "hypothalamicotegmental tract" of Rioch. This author describes it as arising in the ventromedial hypothalamic nucleus and turning caudalward in the H_1 field of Forel.

The supraoptic system runs caudal, medial and backward always skimming the dorsal surface of the chiasm and optic tracts and obtains a very superficial position in the tuber cinereum. Once these main streams of fibres have arrived in the neighbourhood of the median sagittal plane, they become confluent (this is specially clear with respect to groups 2 and 3), interweaving with the fibres of the opposite side. In this way, the commissure of the ventral lip of the entrance area is formed.

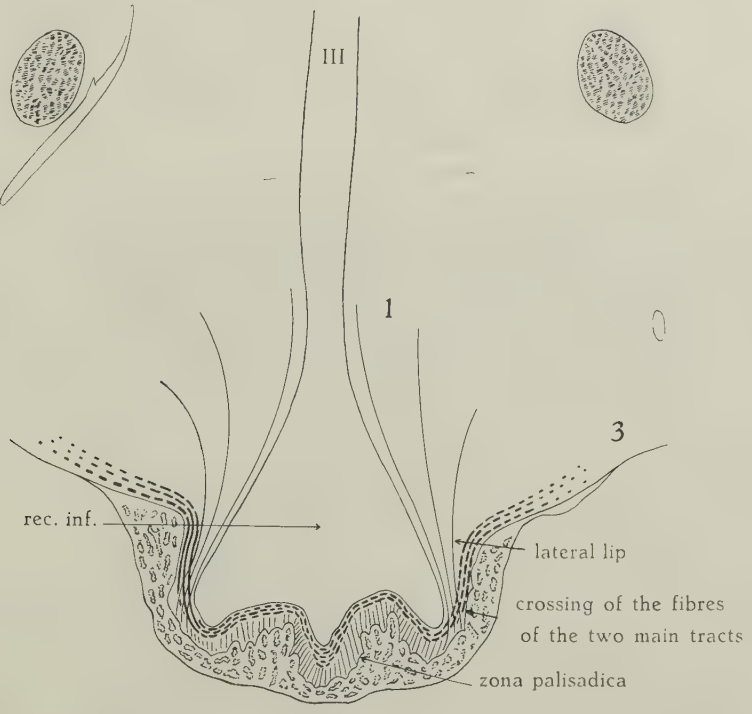


Fig. 31. Drawing from a frontal section showing the lateral lip of the entrance area. 1 = tractus tubero-hypophyseus. 3 = tractus supraoptico-hypophyseus.

The difficult point of the origin of the fibres of the palisade-like system has been carefully examined in series 1140. We think that these fibres have a double origin: they are partly collaterals of the commissural system and partly they belong to the periventricular system. The latter fibres must cross the barrier formed by the commissural system to arrive at the most peripheral subzone of the ventral lip. Some of these crossings have been seen but not as frequently as might be expected. In any case, the palisade-like system of fibres does not extend laterally beyond the area lined by the pars infundibularis.

Summarizing what we have said, it follows that the afferent fibres of the ventral lip can be divided into three main bundles which converge in this part of the entrance area. The ventral lip shows two structurally different zones, one

internal (wedge of the nerve cells of the n. infundibularis) and the other external (radix infundibuli of Nowakowski). The latter may be subdivided again into two subregions: the area of commissural fibres and the area of the palisade-like system (fibres disposed perpendicularly to the former). In spite of the name, the latter fibres have nothing to do with the zona palisadica which does not exist in the ventral lip.

B) *Lateral lip.* The positon of the fibres in the lateral lip is simpler than that of the ventral or dorsal lips. It must be remembered that at this level, the recessus infundibularis is in open communication with the third ventricle. The ventral wall of the infundibulum, forming the floor of the recessus, joins the tuber by means of the lateral wall. The dorsal wall of the infundibulum has not yet appeared because the level is too proximal.

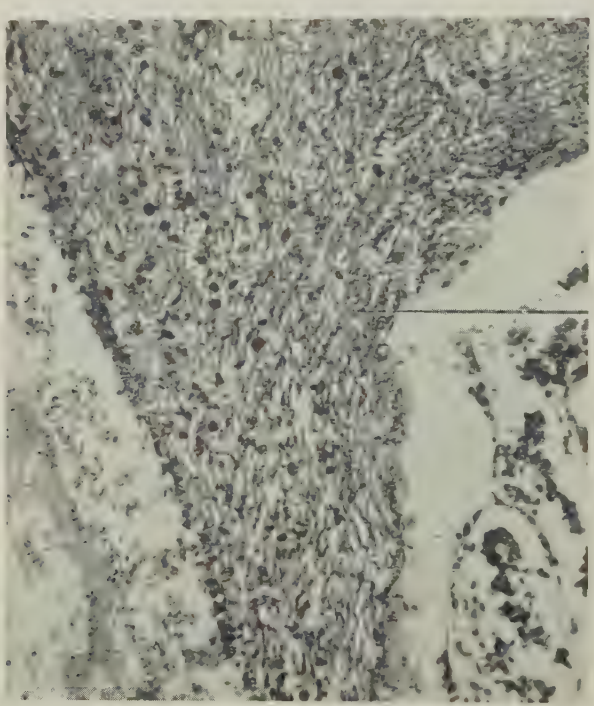


Fig. 32. Lateral lip of the entrance area. (section B of fig. 9). Neg. 8752.

The position of the fibres is schematically indicated in fig. 31. In the same way as in the ventral lip, two zones can be considered in the lateral one. The internal zone, forming the limit of the cavity of the recessus, is constituted by the n. infundibularis wedge zone. It contains small nerve cells and pale-stained fibres issued from the periventricular system. The second zone, peripheral, is in contact with the pars infundibularis of the adenohypophysis. It is formed almost exclusively by nerve fibres (perifornical + supraoptic systems). This is the zona

fibrillaris of our nomenclature. In the lateral lip of the entrance area and in part of the lateral wall, the zona fibrillaris is in contact with the pars infundibularis without any interposition of the zona palisadica (fig. 32).

The nerve fibres of the zona fibrillaris of the lateral lip are disposed in thick bundles, sectioned obliquely. Under high magnification it can be seen that pale, singly-running fibres of the nucleus infundibularis wedge zone penetrate into the zona fibrillaris forming a sharp angle with the bundles of the latter. These fibres do not become part of the bundles of the zona fibrillaris; they only seem to cross this zone on their way to their further destination. The fibres of the zona fibrillaris belong thus to two systems morphologically different: the more obvious is the tractus supraoptico-hypophyseus or group 3 of fig. 28. The second system, much more difficult to see, is the continuation of group 1 of fig. 28 (periventricular system).

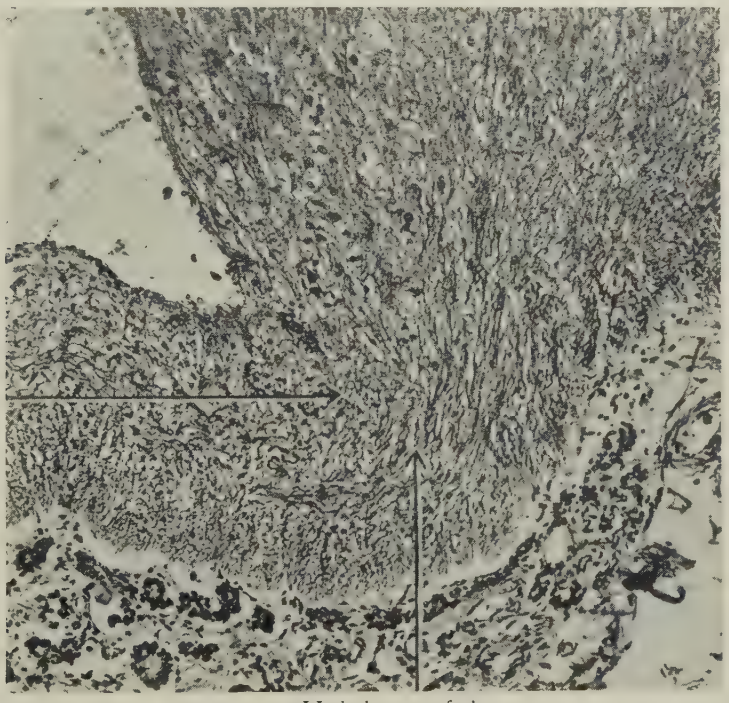


Fig. 33. Nerve fibres in the zona fibrillaris. Note the arrangement in bundles and the small size of the fibres. Obj. 10. Oc. 8. Neg. 7289.

Morphological differences between these two systems are firstly that the supraoptical fibres are grouped in bundles which may contain as many as 16 fibres, whereas the periventricular fibres run separate and secondly, that there are also staining differences between these two systems. The singly running fibres

are in general paler than the supraoptical fibres, but these differences, depending on the general shading exhibited by the sections (and this is very variable), cannot be summarized here. It must be admitted that a very careful examination with an oil-immersion objective is necessary to make the pale fibres of group 1 (periventricular fibres) visible, situated as they are between the more strongly impregnated, thick bundles (not thick fibres) of the tractus supraoptico-hypophyseus.

Fig. 33 shows with great clarity that large bundles of the zona fibrillaris of the lateral lip, after passing along the lateral wall, turn medially to reach the ventral wall. This means that the fibrillar share of the ventral wall originates not only from purely rostral fibres, that is to say, fibres which have entered the neurohypophysis through its ventral lip, but also from lateral fibres. In other words, fibres that ultimately come to lie in the ventral wall and at more distal levels could be taken as belonging to the topographically ventral fibres, are not ventral in the entrance area. The lateral lip (and its prolongation, the lateral wall) may, therefore, be considered as a path for further nerve supply of the ventral wall.

It must be stressed that the majority of the fibres of the tractus supraoptico-hypophyseus enters the neurohypophysis through the lateral lip of the entrance area. They are thus originally lateral fibres. They form by far the greater part of the zona fibrillaris of the lateral lip (and lateral wall). The mass of strongly stained fibres constituting the zona fibrillaris of this area is a continuation of groups 2 and 3 of fig. 28. The continuation of group 1 is to be found in the nucleus infundibularis wedge zone which interposes itself between zona fibrillaris and the lumen of the recessus.

In order to preserve continuity of description we are now going to consider the disposition of the fibres in the proximal portion of the ventral wall. It must be remembered that the n. infundibularis wedge zone also exists in the ventral wall, at least in very proximal areas of it. The stratification pattern of the ventral wall in these very proximal levels is the following: 1., zona ependymalis. 2., n. inf. wedge zone. 3., zona fibrillaris. The normal pattern (that is to say, the pattern of more distal portions of the infundibulum) is: 1., zona ependymalis. 2., zona fibrillaris. 3., zona palisadica. 4., zona granulosa (not existing in the dorsal wall).

The transformation of the ventral lip into ventral wall brings about sudden changes in the position of the nerve fibres. In order to understand them we must bear in mind that the ventral lip of the entrance area forms an angle of approx 90° with the ventral wall of the infundibulum. The result of this abrupt change in direction is that the palisade-like system of the peripheral zone of the ventral lip is now sectioned almost perpendicularly to the axis of the fibres and appears more or less as tiny black dots.

The commissural system of fibres loses its clear, transversal situation and

becomes more and more oblique until its fibres are disposed in a sagittal plane. At this moment, both fibre systems (palisade-like and commissural) are disposed more or less parallel to each other in the ventral wall of the infundibulum. Thus, after a relatively short space, a considerable change in the disposition of the fibres of these two systems has taken place. They were after all perpendicularly disposed in the ventral lip.

The nerve fibres in the zona fibrillaris are very numerous. Many of these fibres are grouped in bundles consisting of 3-16 fibres each. There are also singly running fibres. They are situated predominantly in a very superficial position limiting with the pars infundibularis, and are extremely thin; their thickness, measured with an ocular micrometer, was found to be between $^1/_2$ and $^1/_4$ μ. They do not take the eosin of the Häggqvist staining, which means that they must be considered as unmyelinated, at least in terms of light-microscopy.

In sections stained with the Bodian method, a considerable amount of "optically empty" space is present between the fibre bundles. These spaces indicate either the probable existence of an ependyma fibre running radially from the ependyma towards the pars infundibularis or the presence of connective tissue bundles, stained very faintly — if at all — with this method.

If we look at the fibres contained in the ventral wall of a transversal section made at a very proximal level, we observe that the majority of them run in a more or less sagittal plane and are sectioned perpendicularly. This contingent of fibres represent the confluence of the commissural system and the palisade-like system. An important question arises now: is it possible to distinguish these two systems in silver-stained sections once they have become sagittal? In our opinion this is indeed possible. The fibres which are the continuation of the palisade-like system are almost in contact with the pars infundibularis and run practically isolated, whereas the fibres which are the continuation of the commissural system run grouped in bundles of 3-16 each and are situated in the neighbourhood of the lumen of the recessus. Contrary to the general opinion in the literature on this subject, there are no striking differences in thickness among the axons of these two systems. In the cat, at least, it is not possible to speak of "thick, coarse axons" as is done by almost everybody.

The central zone of the ventral and lateral wall (n. inf. wedge zone) shows a different aspect. It is more cellular and the fibres are more irregularly disposed. A detailed rescription of the different cell types present here is outside the scope of this thesis. It would seem that four categories of cells can be distinguished in the proximal part of the infundibulum: a) the ependyma cells. b) the neuroglia (pituicytes). c) the nerve cells of the n. infundibularis. d) the endothelial cells of the wall of the vessels (very scanty). The staining methods used leave the cytoplasm of these cells completely unstained.

The fibres of the internal zone (n. inf. wedge zone) are so irregularly disposed

that a systematic description of them seems impossible. Their course is extremely irregular; it changes continually in an infinite number of ways. They are not arranged in bundles as the greater part of the fibres in the zona fibrillaris are.

C) *Dorsal lip.* On studying more distal sections, we observe that the slit-like communication between third ventricle and recessus infundibularis grows progressively narrower until the lateral lips become fused in the mid-line. At this moment we are in the dorsal lip i.e., in the attachment of the dorsal wall to the tuber cinereum (pars caudalis tuberis). At a slightly more distal level, the infundibulum becomes completely separated from the hypothalamic floor, forming a very acute angle with it (the sulcus infundibularis), the bottom of which is partially filled by the pars infundibularis.

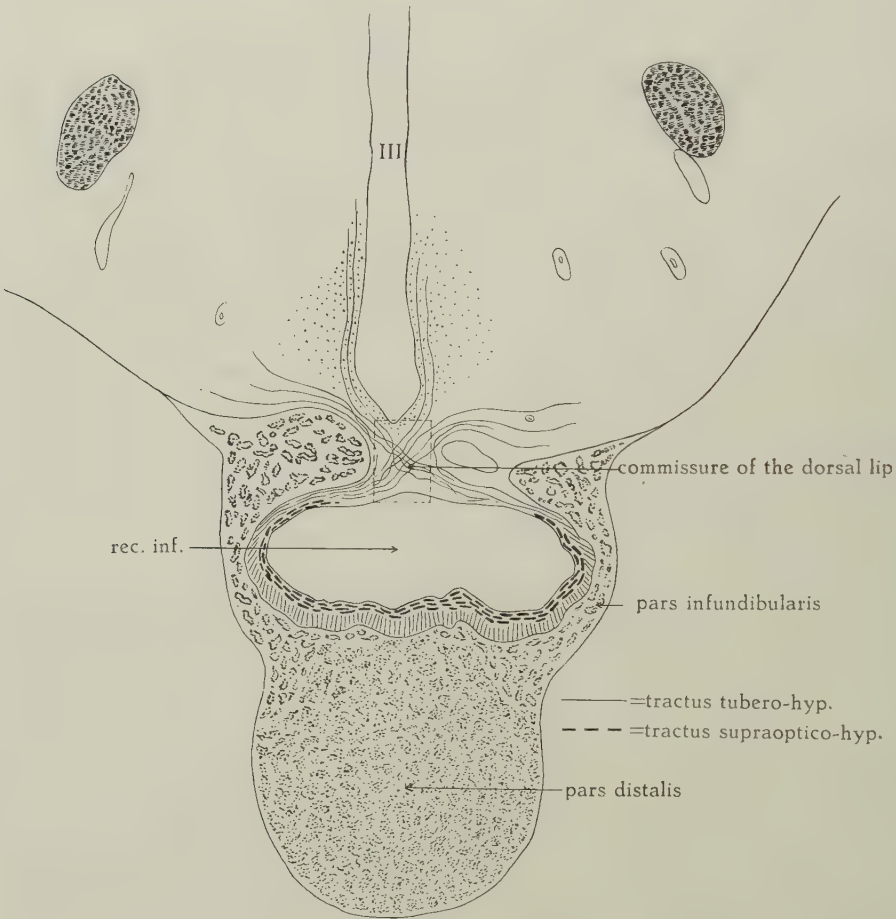


Fig. 34. Disposition of the nerve fibres in the dorsal lip of the entrance area. The area within the rectangle is shown in the following fig. at higher magnification.

The topography of the fibres of the dorsal lip shows some analogies with the ventral one. Two zones may also be distinguished in the dorsal lip; the external one is lined by the pars infundibularis, and is constituted almost exclusively by nerve fibres (fig. 34). The internal zone forms the wall of the third ventricle and is rich in nerve cells which belong to the nucleus infundibularis, in exactly the same way as in the ventral lip. By studying frontal sections we have concluded that the majority of the purely dorsal fibres arrive at the dorsal lip through the pars caudalis tuberis. A cross-section through the dorsal lip shows the transition between pars caudalis tuberis (above) and dorsal wall of the infundibulum (below). It is characteristic that the bundles of dorsal fibres which approach the dorsal lip also send out fibres which, in crossing the mid-line, pass into the other branch of the pars caudalis tuberis (fig. 35). The fibres follow an extremely irregular course here. Part of these decussating fibres seem to enter the dorsal wall from the opposite side. The course of these fibres is almost transversal; they are parallel to the plane of sectioning. Probably these crossing fibres constitute the bundle of transversal fibres which may be observed in the proximal part of the dorsal wall of median sagittal sections.

Fig. 35. Dorsal lip of the entrance area. Obj. 6,3. Oc. 8.

In our material, the nuclei of origin of the purely dorsal system of fibres are very difficult to determine. There are reasons for accepting that the origin of these fibres is not at great distance from the dorsal lip. In accordance with the nomenclature of Fisher, Ingram and Ranson ('32) we believe that these axons originate in the n. hypothalamicus ventrolateralis, n. hypothalamicus posterior and possibly in the lateral hypothalamic area. Adequate staining of these areas

of the hypothalamus is extraordinarily difficult. A certain number of fibres which probably originate in the lateral hypothalamic area cross the mid-line (fig. 36), entering the neurohypophysis at the opposite side from which they come. The posterior part of the nucleus infundibularis also sends considerable number of fibres to the dorsal wall, but these fibres can be seen much better in sagittal sections. The supraoptical fibres do not enter the neurohypophysis through the dorsal lip; they enter mainly through the lateral one. Still we must remember that there are no sharp borderline between lateral and dorsal lips. When we say that the supraoptical fibres do not enter the infundibulum through the dorsal lip, we do not mean that there are no supraoptical fibres in the dorsal wall; in fact, they are very numerous. It should not be forgotten that the dorsal wall of the infundibulum in fact represents lateral and dorsal walls (actually the infundibulum is much broader than the dorsal lip) and we know already that the majority of the supraoptical fibres enter the infundibulum through the lateral lip.

If we summarize the results of this analysis on the topography of the hypothalamic nerve fibres in het entrance area we get the following: the fibres of

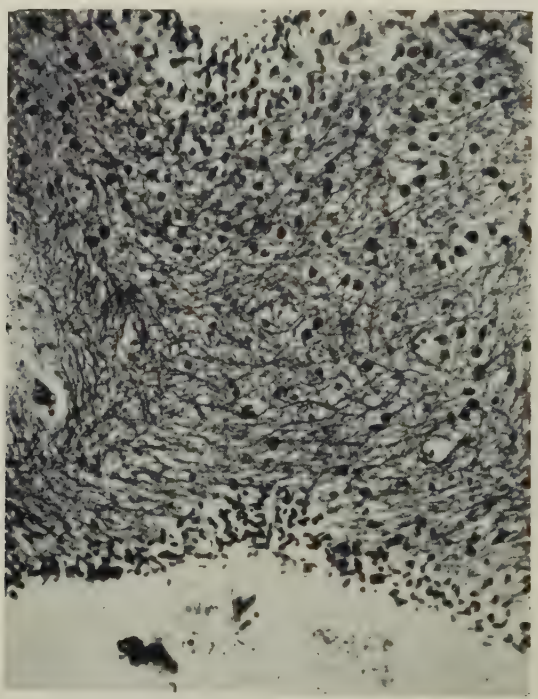


Fig. 36. High magnification of the fig. 35. Obj. 16. Oc. 8. Neg. 8750.

the tractus supraoptico-hypophyseus were found to occupy a very lateral situation in the ventral lip (group 3 of fig. 28). These fibres partly join the bundles of group 2 forming a commissure in the ventral lip.

Group 2 is constituted by fibres coming from the nucleus perifornicalis, paraventricularis and n. hypothalamicus ventromedialis.

Group 1 is constituted by the periventricular system originating in the n. paraventricularis, infundibularis, hypothalamicus ventromedialis and n. ventrodorsalis (?).

The peripheral zone of the ventral lip is to be divided into two sub-zones fig. 30): the internal is occupied by the commissural system of fibres; the external — in contact with the pars infundibularis — is formed by the palisade-like system of fibres. The latter are in part derived from the periventricular system and in part, from collaterals of the perifornical system.

In the lateral lip, the tractus supraoptico-hypophyseus (group 3) is also very laterally situated. No zona palisadica is interposed between this tractus and the pars infundibularis. Fibres other than the tractus supraoptico-hypophyseus, enter the lateral lip through the n. infundibularis wedge zone. These are for the greater part tuber fibres.

The fibres entering the infundibulum through the dorsal lip are to a large extent tuber fibres originating in the n. infundibularis, n. hypoth. ventrolateralis, n. hypoth. posterior and lateral hypothalamic area. Part of these fibres cross the mid-line and enter the dorsal wall from the opposite side.

Very few — if any — supraoptical fibres enter the infundibulum through its dorsal lip. Notwithstanding this, supraoptical fibres can be found in the dorsal wall. This implies that „lip" is not the same as "wall".

The existence of very numerous nerve fibres other than the supraoptical ones in the neurohypophysis has been stressed. The majority of these fibres originate in the tuber cinereum and for that reason, the general denomination "tractus tubero-hypophyseus" may be applied to them. These fibres, with the exception of the palisade-like system of the ventral lip, are always situated close to the lumen of the ventricle in the entrance area. They have, therefore, a central (internal) position. The tractus supraoptico-hypophyseus is on the contrary, always situated in the periphery of the entrance area, in contact with the pars infundibularis.

These observations allow us to distinguish two main systems in the entrance area of the infundibulum; these are:

1. The tractus supraoptico-hypophyseus. The fibres of this system originate in the cells of the n. supraopticus, n. paraventricularis and possibly in other regions more or less far away from the hypophysis (some fibres may come from the fornix, also from the H_1 field of Forel and median forebrain bundle). These fibres enter the infundibulum through the ventral lip and, above all, through the lateral lip. This tractus is constituted by group 3 and, partially, by group 2 of fig. 28.

2. The tractus tubero-hypophyseus. These fibres originate for the greater part in the nuclei of the tuber. The nuclei infundibularis, ventromedialis, para-

ventricularis, hypothalamicus ventrolateralis, hypoth. posterior and lateral hypothalamic area, are the main source of the fibres. This tractus is constituted by groups 1 and, partially, 2. The palisade-like system of the ventral lip belongs also to the tractus tubero-hypophyseus. By far the greater part of the fibres entering the infundibulum through the dorsal lip belong also to this tractus.

The fibres of the tractus tubero-hypophyseus enter, therefore, the neurohypophysis through the ventral, lateral and dorsal lips of the entrance area.

II. THE TOPOGRAPHY OF THE HYPOTHALAMIC FIBRES WITHIN THE INFUNDIBULUM

In the following pages we are going to describe the topography of the hypothalamic nerve fibres which have penetrated the infundibulum through the entrance area. At a proximal level of the ventral wall, the infundibular wall is constituted by 1., zona ependymalis. 2., n. infundibularis wedge zone. 3., zona fibrillaris. In the latter, two systems of fibres may be distinguished: one is situated in the periphery and is the continuation of the palisade-like system described in the ventral lip. These fibres run singly. At this level, no zona palisadica exists. The second system of fibres is situated more internally and is constituted by the tractus supraoptico-hypophyseus.

At more distal levels we observe that the n. infundibularis wedge zone grows progressively smaller. This causes the zona fibrillaris to approach the zona ependymalis until both layers establish the intimate relationship already described in chapter IV. At this moment, the infundibulum, at least in its ventral wall, ceases to be incomplete, since the structural plan which we have described as typical in chapter IV is now established. This does not mean that absolutely no nerve cells of the n. infundibularis can be found at more distal levels, but they are isolated cells which do not constitute a topographical entity.

The nerve fibres of the tractus supraoptico-hypophyseus run more or less sagitally towards the neural lobe. Soon after the disappearance of the n. infundibularis wedge zone, some of the fibres situated closest to the zona ependymalis change their course to get an almost transversal position. Frontal sections show increasingly longer parts of these fibres, thus contrasting with the other fibres of the tractus which being almost perpendicular to the plane of sectioning, are shown only as minute black points (fig. 37).

The transversal system of fibres in the ventral wall is restricted to the medial part of the wall on either side of what we have called sulcus centralis infundibuli. The transversal system is not present in the lateral wall. The fibres lie immediately beneath the ependyma. Not far from the lateral wall, these transversal fibres change their direction abruptly and cannot be traced any further.

As we proceed towards the neural lobe, the transversal system of fibres in the ventral wall becomes less distinct and eventually disappears. This happens

at a level in which the dorsal wall is not yet isolated from the pars caudalis tuberis. We believe that these fibres have previously been longitudinal fibres before changing into transversal ones. In doing so, they pass the mid-line and reach the other side where they probably regain their original longitudinal course after a certain transversal course. This should be taken more as a conjecture than as a confirmed fact.

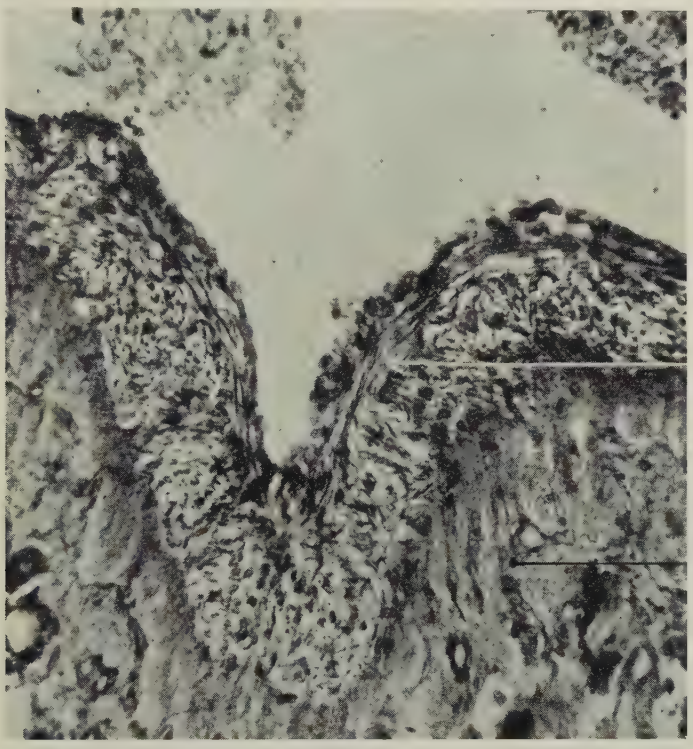


Fig. 37. Transversal fibres in the ventral wall. Obj. 16. Oc. 8. Neg. 8758.

Apart from the transversal system, the course of the nerve fibres offers no peculiarities at these levels. It must be understood that most fibres are slightly oblique to the sectioning plane which causes them to appear as small fragments of fibres instead of as tiny black dots. This is especially clear in the zones close to the lateral wall. Sometimes the obliquity is remarkable and gives the impression of a steady transfer of lateral fibres into the ventral wall (or viceversa). It is, nevertheless, always necessary to allow for the funnel-like shape of the infundibulum which prevents the fibres from running more or less parallel to each other.

The zona palisadica appears for the first time in the ventral wall at certain distance from the proximal limit of the neurohypophysis (sulcus infundibularis). In the beginning it can only be recognized in the medial area of the ventral

wall. Little by little it extends laterally to invest the lateral wall (fig. 12). Further details are given in chapter VI.

The course of the fibres in the ventral wall in these proximal levels, with the exception of the transversal fibres, is very regular. The zona fibrillaris appears in our material as made up exclusively of nerve fibres grouped in bundles which are separated from each other by white (unstained) spaces. Every bundle has 4-12 fibres or more. The thickness of the fibres as seen in sections perpendicular to their axis is surely less than $^1/_2\ \mu$. It might be suggested that the thin fibres grouped in bundles represent neurofibrills rather than axons. This suggestion cannot be accepted for the following reasons:

1. Our search for neurofibrills in the thick axons of our material (fasciculus opticus, nervus oculomotorius) gave only negative results.

2. The arrangement of the bundles of fibres in the infundibulum does not suggest that they are only parts constituting a nerve axon (fig. 38). Very often, these bundles are disposed in rows, leaving unstained spaces more or less rectilinear between them, which are occupied by the interspersed unstained ependyma fibres. In other cases, they form an irregular circle, where, by focusing up and down, they can be seen approaching or separating from each other. They do not suggest a bundle of neurofibrills anywhere.

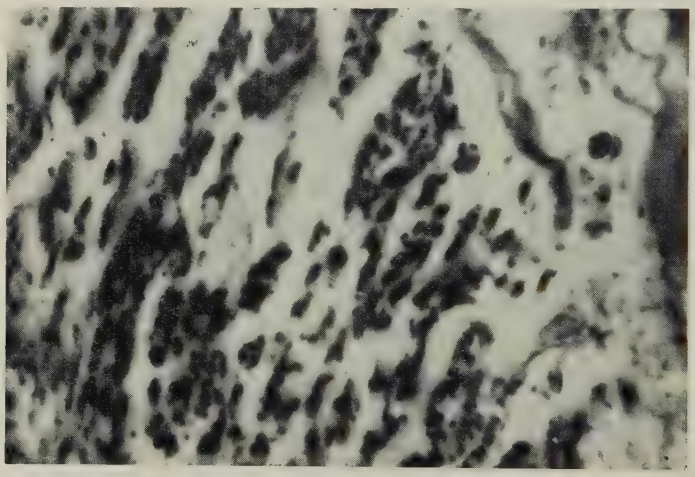


Fig. 38. Obj. 100. Oc. 8. Neg. 8197.

We have not seen a clear distinction between thick and thin fibres in the infundibulum of the cat in spite of a long search with a Neofluar oil-immersion objective ($\times$100) and a Zeiss ocular C ($\times$8 and $\times$12). Of course, to compare the thickness of the fibres we must satisfy two conditions: 1. The fibres must be cut perpendicularly to their axis and 2. They must be normal fibres, not degenerating ones. On the other hand, we have seen very clearly that the arrangement of the fibres is different in the proximal, middle and distal regions of the

infundibulum. The fibres of the zona fibrillaris are arranged in groups in such a way that when studied with low magnification, they give the impression of being individual axons. This impression proves to be wrong when we examine these fibres carefully with adequate optical equipment.

The fibres in the palisade zone, above all in very proximal regions where this zone is not yet clearly constituted (see following Chapter) run practically isolated. This is also the case with those fibres placed in the limit between zona fibrillaris and zona palisadica (above all in the most proximal regions of the ventral wall). On very close examination, some differences can be recognized between these two streams of fibres: in general the fibres of the zona fibrillaris are almost black whereas those of the zona palisadica are reddish. We shall not claim that all these fibres are of exactly the same thickness; on the whole we believe that the central fibres are perhaps slightly thicker than the peripheral ones but this is by no means a striking difference. Furthermore, we can state that in no case have we seen fibres in the infundibulum thicker than $^1/_2\ \mu$ — the majority of them is even thinner (fig. 38). It is evident that the term "thick, coarse axons" so frequently found in the literature on this subject is misleading.

The fibre bundles are not indepedent entities that run up to their ultimate destination preserving their individuality. On the contrary, they continually interchange fibres, i.e., a fibre running in a particular bundle may at a given moment leave it only to be incorporated into another bundle.

Dorsal wall. The course of the fibres in the dorsal wall is more irregular than in the ventral one. In the proximal part of it the zona palisadica is absent (fig. 13). At this level, the zona palisadica still well developed in the ventral wall, attains its maximum thickness in the lateral wall and diminishes sharply in the dorsal one, the most central part of it being completely free from this zone. At this level, therefore, the dorsal wall is formed by a zona ependymalis and a zona fibrillaris. The limit with the pars infundibularis is a sharp one; in azan sections, a thin layer of connective tissue stained in blue can be seen interposed between these two parts.

The course of the fibres in the zona fibrillaris of the dorsal wall is not the same in those fibres placed close to the ependyma and in those close to the pars infundibularis. The first ones are grouped in bundles running obliquely towards both lateral regions of the infundibulum. The fibres situated close to the pars infundibularis are not grouped in bundles but in a completely irregular fashion. These fibres are stained in copper-red showing a colour similar to that of the fibres in the zona palisadica of the ventral wall. In series 1370 (fig. 39), we observe that the reddish fibres break the connective tissue barrier with the pars infundibularis and penetrate deeply into the interstitial spaces between the follicles. A comparison with the following section — stained with azan — excludes every possibility of connective tissue being impregnated. These

Fig. 39. Tranversal section of the dorsal wall of the infundibulum. Nerve fibres penetrate into the pars infundibularis. Obj. 40. Oc. 8. Neg. 8632.

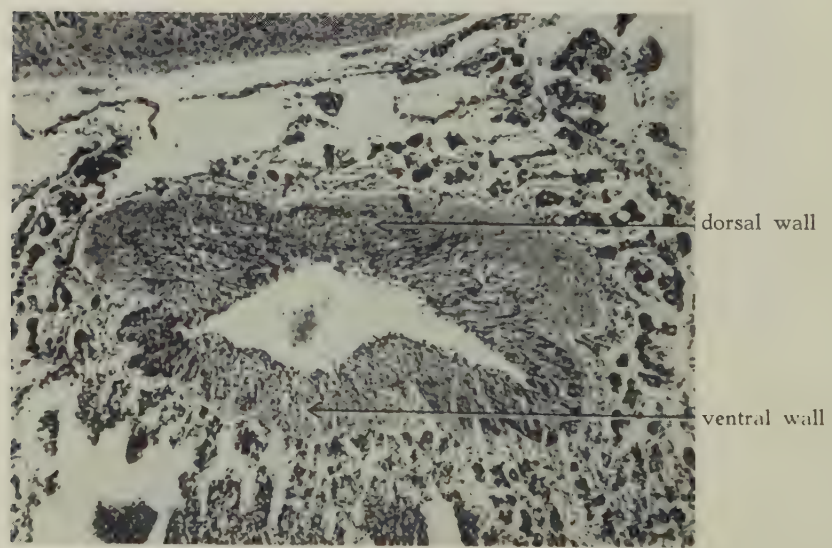


Fig. 40. Transversal section of the infundibulum, shortly before its debouchment in the neural lobe. Note transversal fibres in the dorsal wall. Obj. 6,3. Oc. 8. Neg. 8753.

pictures prove the existence of a hypothalamic innervation of the pars infundibularis. The fibres run along the interfollicular spaces in irregular bundles. They do not penetrate deeply into the parenchyma of the pars infundibularis.

The sections taken at a slightly more distal level show that the most peripheral part of the dorsal wall becomes progressively more stained in violet. What happens actually, is that the interfibrillar spaces which are always perfectly unstained in the zona fibrillaris, become progressively more violet coloured, which gives the zone quite a different aspect from that of the zona fibrillaris. At this moment, the zona palisadica of the dorsal wall has appeared.

The fibres of the zona fibrillaris situated close to the zona ependymalis become progressively more oblique until they reach a completely transversal situation (fig. 40). In these sections, the zona fibrillaris is formed by a system of transversal fibres, in contact with the ependymary lining of the recessus, and a system of longitudinal fibres limiting the zona palisadica (fig. 41).

The transversal system of fibres in the dorsal wall is present only over a short extension. It disappears before the termination of the lining of the pars infundibularis. It was not possible to determine the further course of these fibres; in our opinion only very small experimental lesions in the infundibulum can give a satisfactory answer to this question.

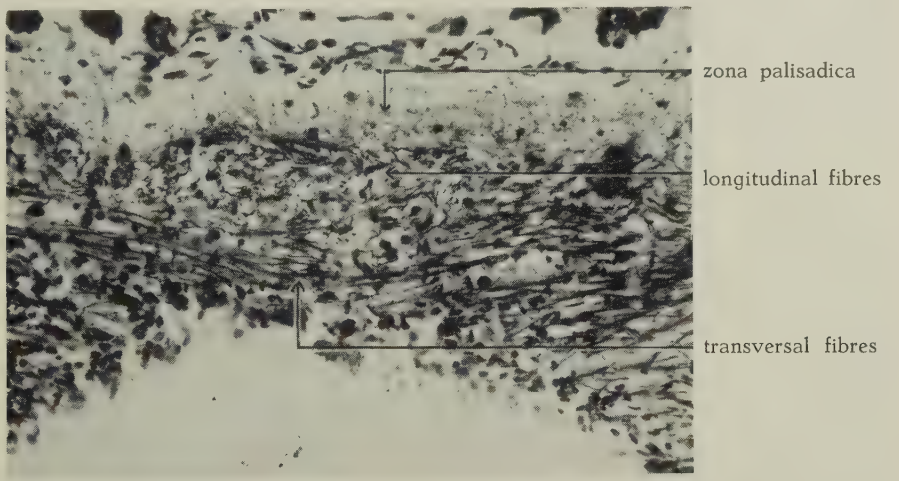


Fig. 41. High magnification of the above fig. Obj. 25. Oc. 8. Neg. 8817.

At more distal levels of the dorsal wall, the fibres are seen to run in parallel bundles in the same way as in the ventral wall. A comparison with the latter shows that the only criterion for distinguishing these two groups of fibres is the greater irregularity of the course of the dorsal wall fibres. No differences in thickness between these fibres have been found. The arrangement in bundles is also less marked in the dorsal than in the ventral wall. This is especially clear in proximal levels. In distal ones, on the contrary, the fibres show exactly

the same characteristics.

The extension of the zona palisadica in the dorsal wall is small. Before the beginning of the lining of the pars intermedia, this zone is already reducing its thickness. When the pars intermedia comes into contact with the dorsal wall, no trace of the zona palisadica can be seen.

Further distally the transversal diameter of the infundibulum is considerably smaller. In series 1370, the dorsal wall becomes several times thicker than the ventral one. This causes the wall to bulge into the cavity of the recessus infundibularis which is now reduced to a slit-like space. Numerous Herring bodies and possibly some nerve terminals are found in this area.

In the following sections we arrive at a level immediately in front of the neural lobe. All nerve fibres in the dorsal wall are arranged in bundles. The twisting and looping fibres so frequently found in the proximal levels of the dorsal wall have disappeared at this level. Here, only "regular" fibres remain.

Lateral wall. The delimitation of the lateral wall in our topographical scheme is a difficult point. In the infundibulum proper, the lateral wall is obviously that small part of the wall joining the dorsal with the ventral wall and closing laterally the lumen of the recessus. In more proximal parts of the infundibulum, in the entrance area, the lateral wall is that part of the infundibular wall joining the lateral lip with the most lateral part of the ventral wall. A difficulty arises when we see that the lateral wall in the entrance area is much longer than in more distal levels of the infundibulum. It is evident that part of the primitive lateral wall is gradually absorbed by the future dorsal wall.

The fibres contained in the lateral wall are rarely — if ever — perpendicular to the plane of sectioning. This is understandable to a certain extent, if we remember the conical shape of the infundibulum; the most lateral fibres are also the more oblique. Nevertheless, often fibres are found which lie in an almost transversal plane, and they can be traced over some distance. Some of these fibres can be seen to turn from the dorsal into the ventral wall, i.e., one of the cut ends of the fibre is situated in the dorsal wall whereas the other is situated in the ventral one (fig. 42). In this fig., one of these fibres has been illustrated; we believe that many fibres follow the same course. Of course, the obliquity of the fibres with respect to the plane of sectioning is such that the probability of getting many equally convincing pictures is not great. The majority of the fibres are present for shorter distances in the sections, but they give exactly the same impression.

The lateral wall must be considered as a transition zone which the fibres pass through before reaching their ultimate destinations. It must be acknowledged that the direction of the streaming cannot be established by microscopic observation alone; the fibres might be also ventral fibres going to the dorsal wall instead of the other way around. I think the latter is more probable, because of

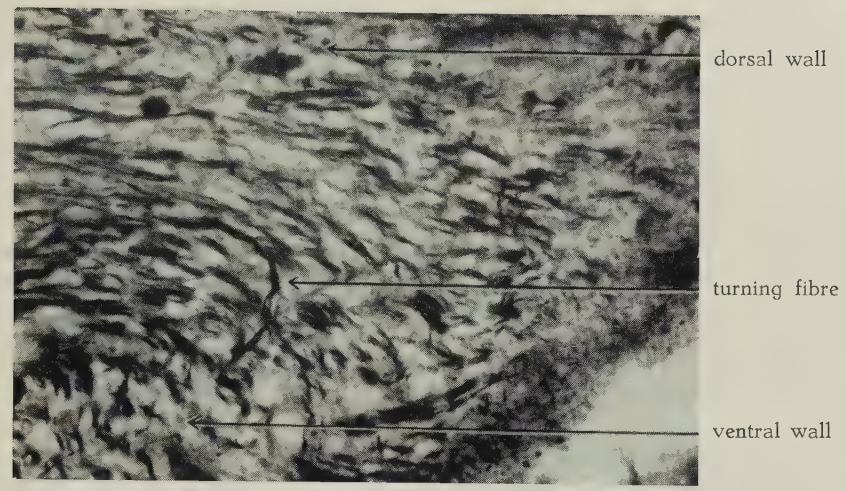


Fig. 42. Transversal section showing the lateral wall of the infundibulum. Note fibres passing from one wall to the other. Obj. 40. Oc. 8. Neg. 8306.

the greater obliquity of the fibres in the dorsal wall. Actually, what seems to me of importance, is the fact that the hypothalamic fibres in the infundibulum do not occupy a fixed and invariable position along their entire course to the neural lobe. A fibre situated in the lateral wall of the infundibulum at a proximal level, may change its position (the majority of them do) at more distal levels to enter the ventral wall. There is thus a continual variation in the topographical position of these fibres. An exact analysis of these positional changes is not practicable in normal material.

III. THE AREAS OF TERMINATION OF THE FIBRES IN THE NEUROHYPOPHYSIS

Two morphologically different hypothalamic systems have been distinguished in the neurohypophysis of the cat: the tractus tubero-hypophyseus and the tractus supraoptico-hypophyseus. The former is constituted by isolated running fibres showing some staining differences when compared with the supraoptical ones. The tuberal fibres may also be distinguished by the great irregularity of their course; the fibres loop and twist, forming whorls, angles etc. within very short distances. In contrast with this, the fibres of the tractus supraoptico-hypophyseus have an almost straight – now and then somewhat undulating – course.

A close analysis of that portion of the infundibulum situated immediately proximal to the neural lobe reveals that all fibres arriving at the neural lobe are – typically – grouped in bundles, showing all the characteristics of the supraoptical fibres. This is not only true of the ventral wall but also of the dorsal one. We are convinced that no tuberal fibres arrive at the neural lobe. It can safely be said that they become exhausted in more proximal parts of the

neurohypophysis; in reality, the area of termination of these fibres is the zona palisadica of the infundibulum. In the following chapter we shall study the topography and course of the tuberal fibres. We here refer to the supraoptical ones.

A transversal section of the infundibulum shortly before the beginning of the processus infundibularis shows it as an ellipse. In examining more distal sections, we observe that the dorsal wall increases its convexity and forms an angle which at more distal levels becomes even sharper. The vortex of the angle (fig. 43) is directed upwards, towards the mammillary bodies. The dorsal wall is thus, divided into two symmetrical halves. Little by little, the dorsal fibres become more oblique with respect to the plane of sectioning, which facilitates their passing into the peripheral zone of the neural lobe.

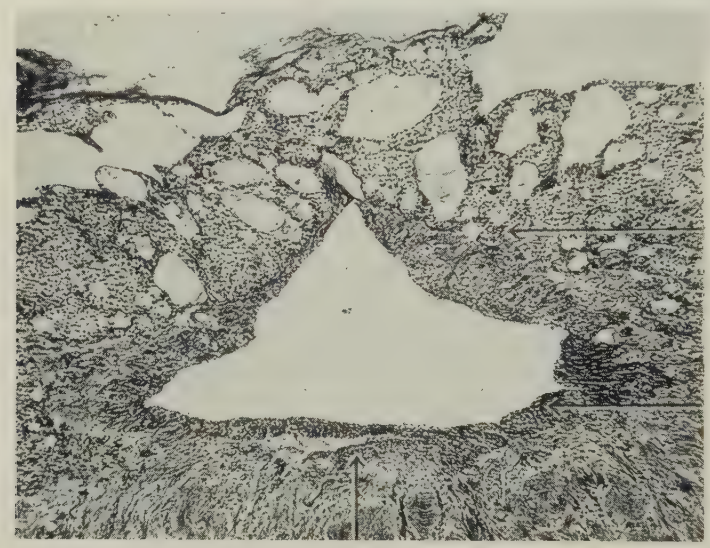


Fig. 43. Transversal section of the neural lobe, showing the central zone and the zona lobularis. Note that the latter is not present at the roof of the neural lobe. Obj. 6,3. Oc. 8. Neg. 8760.

The greater part of the fibres of the tractus supraoptico-hypophyseus terminate in the dark areas (Verdichtungszonen of Romeis) of the neural lobe. These endings are histologically difficult to demonstrate and they shall not be studied here. A number of fibres of this tractus end in the zona fibrillaris of the infundibulum, i.e., before arriving at the neural lobe. Frontal sections demonstrate that the fibres arriving at the neural lobe through the ventral wall are distributed in the ventral (caudal) part of it. Most of he fibres have entered the infundibulum through the lateral lip and are first situated in the lateral wall, from which they pass to the ventral wall.

It has been pointed out that at distal levels, the dorsal wall of the neurohypophysis is bent into two symmetrical branches. These branches become in-

vested by the lateral, peripheral part of the processus infundibularis. The degree of this investing process is subject to considerable individual variation.

Now the following question arises: What is the destination of the fibres contained in the dorsal wall of the neural lobe? By far, the greater number of them pass into the "light areas" (Zwischenstreifen) of the peripheral zone of the neural lobe on their way to the "dark areas" (Verdichtungszonen). The fibres situated in the vortex of the angle (fig. 43) either become oblique and descend to a more lateral position to be able to enter the "light areas" or terminate as Herring bodies in the rudimentary portion of the roof of the neural lobe (fig. 44).

Fig. 44. Rudimentary portion of the roof of the neural lobe. Obj. 16. Oc. 8. Neg. 8759.

The study made in the preceding pages on the course of the hypothalamic fibres enables us to try to answer the problem proposed on page 66. From the description given, the following correlation can be forwarded:

ENTRANCE AREA		INFUNDIBULUM		NEURAL LOBE	
ventral lip	= supraop. + tuberal fib.	ventral wall	= supraop. + tuberal fib.	ventral wall	= supraop. fibres.
dorsal lip	= tuberal fib.	dorsal wall	= supraop. + tuberal fib.	dorsal wall	= supraop. fibres.
lateral lip	= supraop. + tuberal fib.	lateral wall	= supraop. + tuberal fib.	lateral wall	= supraop. fibres.

We have shown that there is a decussation of fibres originating in the nucleus supraopticus and in other nuclei of the hypothalamus (group 2 of fig. 28). By means of these fibres — the commissural system of the ventral lip — it is possible that the centra situated on one side of the hypothalamus exert influence on the

opposite side of the neural lobe. Nevertheless, when we consider what we have said on p. 21, viz., that the hypothalamic fibres do not occupy a fixed and invariable position during their entire course through the infundibulum, it would be very risky to state that the supraoptic fibres which have crossed the mid-line in the ventral lip arrive at the opposite side from which they originate. They might also return to the original side through the lateral wall.

The majority of the supraoptical fibres are, in fact, homolateral. We believe that no large-scale transfer of ventral fibres occurs.

We could ask ourselves what the destination of the fibres contained in the ventral and dorsal wall of the infundibulum is. In order to answer this question, it is essential to make a sharp distinction between fibres following a more or less regular course (the tractus supraoptico-hypophyseus) and fibres following a very irregular course (the tractus tubero-hypophyseus).

Destination of the fibres of the dorsal wall

a). The supraoptical fibres may pass towards the ventral wall through the lateral one. b). They may continue their way to the neural lobe, where they terminate in the dark areas (Verdichtungszonen) of its lateral part. c). They may end in the zona fibrillaris of the dorsal wall as Herring bodies.

The tuberal fibres of the dorsal wall end in the following ways: a) they are involved in the innervation of the ependyma (?); b) They end in the zona palisadica of the dorsal wall and in the pars infundibularis; c) they may pass toward the ventral wall through the lateral wall.

Destination of the fibres of the ventral wall

The "regular fibres" (tractus supraoptico-hypophyseus) terminate for the greater part in the dark areas (Verdichtungszonen) ot the ventral wall of the peripheral zone of the neural lobe. Many fibres also enter the lateral part of the neural lobe.

The "irregular fibres" tractus tubero-hypophyseus) end in the zona palisadica of the ventral wall. Some fibres enter the pars infundibularis of the adenohypophysis.

A number of 'regular fibres" of the ventral wall may also end inside the zona fibrillaris as Herring bodies.

From the precedent description it is clear that only "regular", i.e., supraoptical fibres reach the neural lobe. The fibres of the tractus tubero-hypophyseus on the contrary, terminate in more proximal parts of the neurohypophysis (zona palisadica) or in the pars infundibularis of the adenohypophysis. No hypothalamic fibres have been found to enter the pars distalis. These negative results should not be considered conclusive evidence against the possibility of the hypothalamic nerve supply of the pars distalis. This remains an open question.

Series 1366 and 1367. These series were stained with the Häggqvist method. As was expected, the method failed to show any myelin sheath around the axons. These are stained deep blue and appear grouped in bundles. Silver impregnations give a much clearer picture of the thin hypothalamic fibres in the infundibulum than this method.

The connective tissue sheaths of the capillary loops and the ependyma fibres are clearly displayed in these series. The blood vessels of the ventral wall of the infundibulum can be divided into two sorts: short and long ones. The former do not reach beyond the zona palisadica, whereas the latter penetrate as far as the immediate neighbourhood of the zona ependymalis.

The study of this material conclusively proves the existence of a IV layer in the proximal region of the ventral wall of the infundibulum. Here the ventral wall is formed by 1, the zona ependymalis, 2, the zona fibrillaris, 3, the zona palisadica and 4 this new zone which, following Hagen (whose description was based on the dog), we call "zona granulosa". In general the IV layer takes the methyl blue more strongly than the zona palisadica and is more densely built. Numerous capillaries are placed between these two layers. The walls of these vessels are rich in connective fibres forming a clear barrier between III and IV layer (fig. 21). This barrier is perforated: 1. by the "long" capillary loops which penetrate as far as the zona ependymalis, 2 by the terminal arborization of the ependyma fibres issued from the zona ependymalis, 3 perhaps by nerve fibres. The presence of nerve fibres in the IV layer cannot be established with certainty in these Häggqvist sections.

The IV layer is poor in cells, in sharp contrast with the adjacent pars infundibularis. Numerous bundles of connective fibres issued from the capsule of the blood vessels are present. In silver-stained sections, the structure of the latter also shows differences with the zona palisadica. The nerve fibres have almost disappeared and the structures are outlined vaguely. We have the impression that the IV layer is constituted by structures with very little affinity for the silver staining. It is probable that connective tissue of the pars infundibularis (and of the wall of the vessels) and the terminal arborizations of the ependyma fibres play a prominent rôle in the constitution of the zona granulosa (fig. 21).

Series 1604 and 1601. Three weeks old cats were used for these series. The most interesting point of this material is the clear separation of two zones in the processus infundibularis. The internal zone lies around the lumen of the recessus and represents the distal prolongation of the infundibulum (zona ependymalis and zona fibrillaris). The external one is constituted by the tissue characteristic of the neural lobe, i.e., the "light and dark" areas of Herring. The limit between these two zones in the processus infundibularis is very clearly indicated by that system of vessels which in the infundibulum is placed between zona palisadica and zona granulosa or pars infundibularis (fig. 21). This system

of vessels is known as the "mantle-plexus". It can easily be demonstrated (fig. 25) that the mantle-plexus continues in the neural lobe, separating the internal zone from the external one. Further distally, the infundibular fibres break this vascular barrier on their way to the "light areas" and the "dark ones". Nevertheless, even at these very distal levels, the vascular barrier is still visible to a considerable degree (fig. 26). Further details of the blood vessels in the cat-hypophysis are available in chapter VI.

Information concerning the number of nerve fibres contained in the neurohypophysis is very sparse in the literature. According to Rasmussen, the pituitary stalk of man contains about 70000 fibres. Romeis ('40) was inclined to think of this estimate as being too low. The former scientist counted also the number of cells in the nucleus supraopticus obtaining a total number of 130000 supraoptical cells aprox. The number of supraoptical cells has been counted in other species also (rat, dog), but nothing is known about the number of fibres in the neurohypophysis of these species. It is evident that reliable counts of the hypothalamic cells (n. supraopticus, n. paraventricularis, nuclei of the tuber) and nerve fibres in the neurohypophysis should be of importance for a better understanding of the innervation of the latter.

The only counting of the fibres in the neurohypophysis of the cat — as far as we know — is that of Rumbaur ('50). She estimated the number of these fibres as being between 15000 — 20000.

Nerve fibres must be counted on cross-sections made as exactly perpendicular as possible to the direction of the fibres. When the sections show a high degree of obliquity (or in sections made parallel to the direction of the fibres) then the number of the fibres counted is not reliable because they are overestimated. We have, therefore, chosen the narrowest part of the infundibulum, i.e., the debouchment of the infundibulum into the neural lobe, to perform the counting. At this level, the fibres of the tractus tubero-hypophyseus are eliminated, because they terminate in the zona palisadica, i.e., in more proximal levels. These fibres course very irregularly, their elimination being therefore desirable. The fibres counted belong thus to the tractus supraoptico-hypophyseus.

Attempts at classifying the axons according to their respective thickness failed, owing to the extreme thinness of the fibres. It can be stated that 90% of the fibres have a diameter of $^1/_2\ \mu$ or less. The differences of thickness between the axons are, therefore, too small to allow a proper analysis with the light microscope. The grouping of the axons in thickly-packed bundles caused some difficulty when counting; it was often difficult to tell how many axons constitute a particular bundle, the resolving power of the oil-immersion lenses being sometimes insuffcient (on 8 μ sections) to decide on this question.

It has not been our intention to make a fibre-analysis proper of the infundi-

bular axons. In consequence what follows should be taken as an approximation rather than as established evidence of the number of fibres present in the neurohypophysis.

The great number of nerve fibres in the infundibulum precludes counting all fibres present there. Sampling is to be applied instead, since the results of this method are more accurate than direct counting of all fibres. We had the impression (which proved to be incorrect later) that the fibre density in the dorsal wall of the infundibulum was less than that of the ventral wall, and hence, we counted six samples, three in the ventral wall and three in the dorsal one. This represent a considerable part of the total area of the infundibulum on a cross-section.

The countings were made using a net-ocular micrometer (Schenk '57, modified by Noorduyn) and a Neofluar oil-immersion objective (x100). After counting, the total area of the region in which the samples were counted was measured. This was done as follows: the section in which the countings had been performed was projected on millimeter paper by means of a microscope provided with Abbe drawing chamber under a magnification of 250. This permitted accurate measurement of the total area of a cross section of the infundibulum. When the surface area had been determined, the total number of fibres could be determined by multiplication with the formula:

$$\frac{a}{c} \times b = x$$

a = total surface of the infundibulum in m/m^2
b = total number of fibres counted.
c = counted area of the infundibulum in m/m^2.
x = total number of fibres present in the inf.

The counting was performed on two of our transversal series, i.e., series 1370, 75–2–9; and series 213, 15a–2–5.

RESULTS. Series 1370. Ventral wall : 930. 812. 1084.
Dorsal wall : 643. 560. 721. $b = 4750$
Total area of the section in $m/m^2 = 9378$.

$$x = \frac{9378}{2400}\ 4750 = 17828 \text{ fibres.}$$

Series 213. Ventral wall : 948. 1020.
Dorsal wall : 933. 891. $b = 3792$.
Total area of the section in $m/m^2 = 6886$.

$$x = \frac{6886}{1600}\ 3792 = 16250 \text{ fibres.}$$

If we compare the number of fibres per sample in the ventral and in the dorsal wall of series 1370 we may arrive at the conclusion that indeed, the fibre density in the ventral wall is higher than that in the dorsal one. This is due

to the fact that this series, shortly before the debouchment of the infundibulum into the neural lobe shows a thicknening of the dorsal wall which contains large numbers of Herring bodies and connective tissue fibres. This increases considerably the interfibrillar space and consequently, the fibre density decreases. In series 213, the dorsal wall is completely normal, showing few Herring bodies and no thickening whatsoever. In this series, the fibre density in both walls of the infundibulum is practically the same.

SAGITTAL SERIES

Immediately behind the optic chiasm, the Gudden and Ganser commissures are seen cut perpendicularly. These fibres contrast clearly with the chiasmatic ones owing to their smaller diameter. The supraoptical fibres can be traced looping over the dorsal border of the chiasm. In their course downwards, they become interspersed with the fibres of the supraoptical commissures from which they can be distinguished by their direction and staining characteristics. This component of the tractus supraoptico-hypophyseus, palely stained in this series, seems to connect the pars anterior of the nucleus supraopticus with the pars posterior which is that part of the nucleus which lies in the pars oralis tuberis.

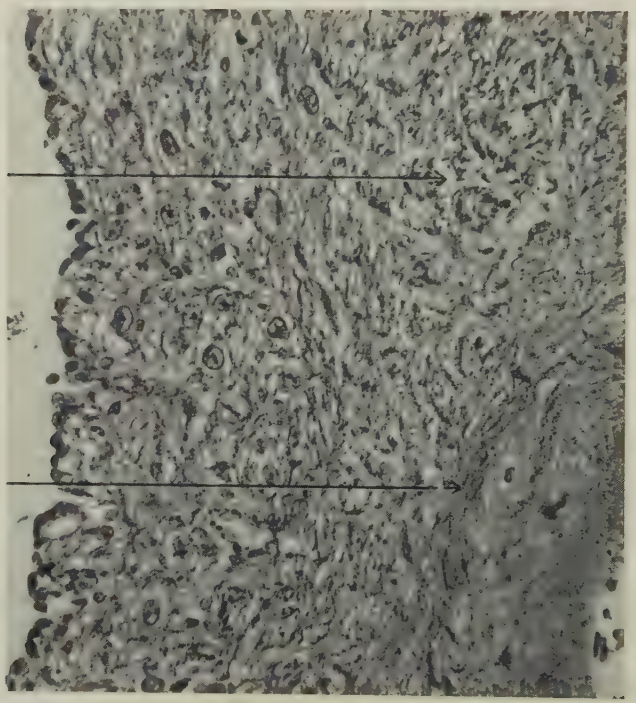


Fig. 45. Sagittal section of the neurohypophysis showing the ventral lip of the entrance area. Obj. 25. Oc. 8. Neg. 8771.

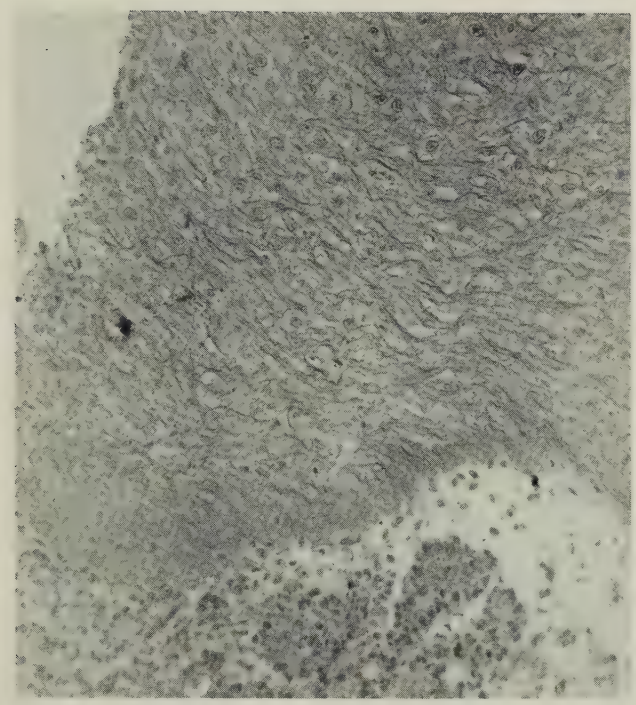


Fig. 46. Paramedian section of the ventral lip. Obj. 16. Oc. 8. Neg. 8772.

At least part of these fibres stop inside the pars posterior, or in any case, they cannot be followed any longer.

An exact analysis of the course of the nerve fibres in the ventral lip of the entrance area proves to be extremely difficult. In the external zone of the ventral lip two systems of fibres can be distinguished: one is completely superficial, corresponding with the palisade system described in frontal sections, whereas the other appears more or less perpendicularly cut and corresponds with the commissural system described in the frontal series.

A closer analysis of the ventral lip reveals differences between median sagittal sections and parasagittal sections (cf. fig. 45 and 46). In purely sagittal sections, the transversal (commissural) fibres are cut perpendicularly and are seen as black dots and the palisade system appears more or less independent from the other system. The latter fibres are stained very palely, contrasting strongly with the commissural fibres which are black. Interspersed between the groups of black dots are short fragments, of pale, thin fibres belonging to group 1 (periventricular system) which crosses the barrier, formed by commissural fibres, to join the palisade system. This is in agreement with our description on p. 72. It must be admitted that these crossings are not on a large scale and are overlooked very easily, owing to the extreme paleness of these fibres.

The situation is different in parasagittal sections. The commissural system is

not cut perpendicularly but obliquely, which enables us to trace the course of the fibres for short extensions. This course is complicated, with many loops and twists. At this level, the "palisade system of fibres" does not exist, its place being occupied by fibres belonging to group 3, i.e., the most lateral group of supraoptical fibres. In a paramedian section, the majority of the fibres belong to groups 2 and 3. Group 1 may be recognized and located with accuracy in median sagittal sections. The continuation of this bundle in the ventral lip is to be found in close contact with the pars infundibularis, interposing itself between the latter and the tractus supraoptico-hypophyseus.

With the exception of the purely median sagittal fibres of the ventral wall, the others are disposed obliquely from lateral to medial, converging toward the mid-line. This is very clear in distal areas of the infundibulum, where by focusing up and down we can see the fibres incurvating toward the median plane.

In distal regions of the infundibulum (ventral wall), the zona palisadica tapers out and disappears. At this level the zona fibrillaris is much thicker than in proximal levels, which gives the impression that the number of fibres present has increased considerably. Nevertheless, it must be remembered that the transverse diameter of this part of the ventral wall is only one third of that of proximal levels – which may be the explanation. In series 589 the fibres in the distal part of the ventral wall are stained more heavily than they are in the proximal part of it.

Lateral lip. In paramedian sections, the attachment of the dorsal wall in the tuber cinereum represents the lateral lip of the entrance area. The dorsal lip appears only in median sagittal sections and is visible in a small number of sections.

The nerve fibres which enter the neurohypophysis through the lateral lip belong to groups 2 and 3 (tuberal and supraoptical fibres) after which they are in the lateral wall of the most proximal part of the infundibulum. Part of these fibres are directed towards the ventral wall (see p. 76) and the rest remains in the dorsal wall, until they arrive at the lateral part of the neural lobe.

Dorsal wall. The dorsal wall is the continuation of the pars caudalis tuberis; between these two regions the sulcus infundibularis penetrates deeply, its cavity being partly filled by the pars infundibularis. The limit between pars caudalis tuberis and dorsal wall is indicated by the disappearance of the glial lining of the base of the brain (Nowakowski, '51).

Some data concerning the histological constitution of the pars caudalis tuberis were given in chapter III. The small nerve cells of this region correspond with what Rioch and Fisher etc. call nucleus periventricular posterior, whereas Nowakowski ascribes this group of cells to his n. infundibularis. The cells are

very small with scanty, somewhat foamy cytoplasm and a certain tendency to bipolarity, the main axis of the cell being disposed more or less vertically. The area close to the pars infundibularis is practically free of cells; in silver-stained sections it appears formed by a system of sagittally directed fibres, running parallel to the inferior surface of the pars caudalis tuberis. This system can be

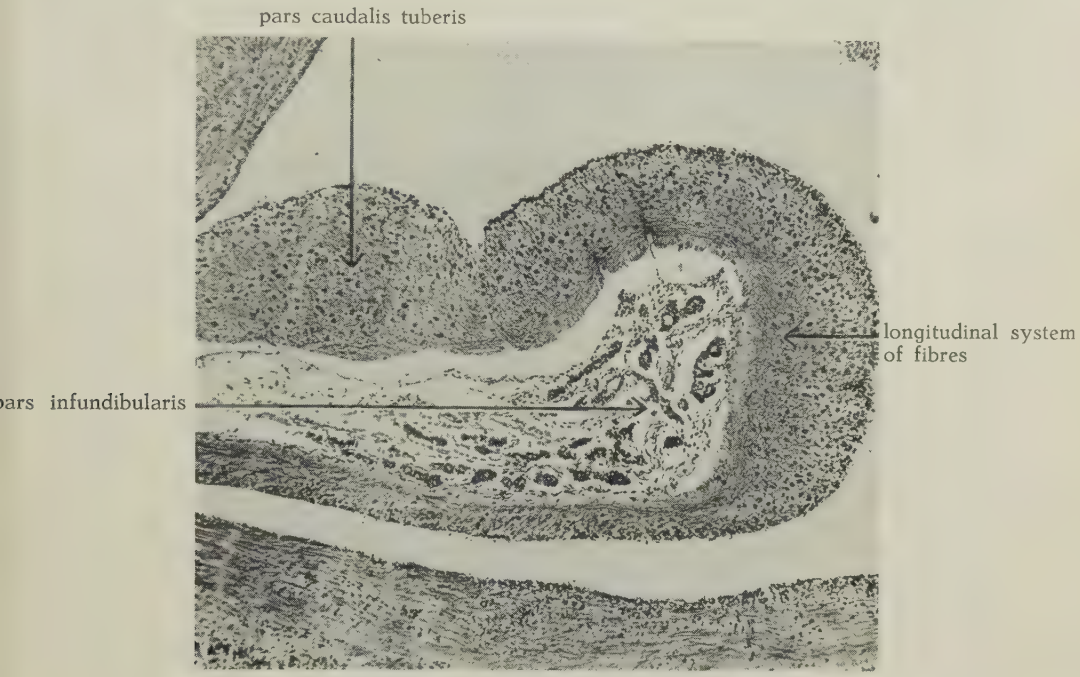


Fig. 47. Median sagittal section showing the dorsal lip. Bodian stain. Obj. 6,3. Oc. 8. Neg. 8775.

seen clearly in fig. 47. Dorsally, it does not extend along the whole extension of the pars caudalis tuberis; on the contrary, about mid-way between the mammillary bodies and dorsal wall it disappears. With strong magnification, many fibres can be seen to become transversal in this area and are sectioned perpendicularly. This corresponds with the transversal systems of the dorsal lip represented in fig. 35.

The disposition of the nerve fibres in the dorsal wall of sagittal sections is comparatively simple. It is not exactly the same in median sagittal sections as in parasagittal ones. In the former, two large groups of fibres may be distinguished in proximal levels (fig. 48): the peripheral one is the continuation of the sagittal system of fibres which we have described in the basal surface of the pars caudalis tuberis. This system continues without interruption along the dorsal wall and is almost in contact with the pars infundibularis. The rest of the fibres of the proximal part of the dorsal wall is placed transversally, which makes them appear as tiny black points. This arrangement holds over a certain

extension until, at a certain level more or less corresponding with the beginning of the pars intermedia lining, all fibres become practically sagittal, continuing their way towards the neural lobe.

In paramedian sections the disposition of the fibres is different. The majority of them are supraoptical fibres which penetrate into the neurohypophysis through the lateral lip. It should be remembered that the dorsal lip is small and because of this paramedian sections are apt to show the lateral lip instead of the dorsal one. Of course, no sharp delimitation can be established between these two lips.

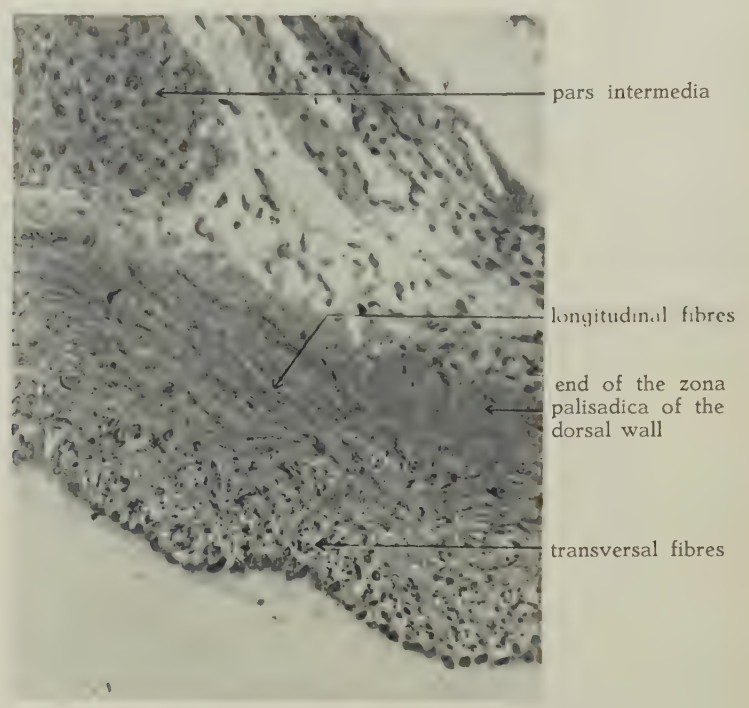


Fig. 48. Sagittal section showing longitudinal and transversal fibres in the dorsal wall of the infundibulum. Obj. 25. Oc. 8. Neg. 8778.

The existence of large bundles of transversal fibres in the dorsal wall of the infundibulum in median sagittal sections (fig. 18) has been stressed. We wonder what the origin and termination of these fibres is. A satisfactory answer to this question is not easy. The tracing of fibres following a complicated course by means of neurofibrillar methods in normal material is very risky. We think that the transversal system of fibres is the continuation of the decussating fibres in the dorsal lip of the entrance area. These fibres come either from the left or right half of the tuber and, crossing the mid-line, pass to form part of the transversal, periependymal system of fibres. Some of them might be engaged in the innervation of the ependyma itself.

The destination of these fibres is also difficult to ascertain. In conformity with transversal sections, it can be easily observed that these transversal systems are only present in the median region of the dorsal wall in close contact with the ependyma. Beyond this medial zone, the transversal fibres disappear. It is evident that they pass to be incorporated into the longitudinal bundles, but after this incorporation they are lost among the mass of longitudinally running fibres and they cannot be traced any further.

HORIZONTAL SERIES

A detailed description of the course of the nerve fibres in horizontal series would force us to repeat the greater part of what has been described already in connection with the transversal and sagittal series. Sections parallel to the infundibular axis may show the course of the nerve fibres over a considerable distance. These series allow us to verify that the course of the fibres in the proximal part of the infundibulum is always much more irregular than in the narrow part of it. In this part, the fibres run regularly arranged in bundles which situation is preserved as far as the neural lobe. It may be interesting to remark that the fibres are more heavily stained with silver in the distal part of the infundibulum than in the proximal one.

Very frequently, fibres situated in the right half pass to the left and viceversa (fig. 16). This happens not only in the dorsal but also in the ventral wall. Nevertheless, the number of fibres which cross the mid-line is not considerable in any given place.

The transfer of originally lateral fibres into the ventral or the dorsal wall can easily be substantiated in these series. The numerous fibres which may be seen entering the neurohypophysis through the lateral lip of the entrance area, are forced shortly afterwards to abandon the lateral wall, which because of the flattening undergone by the infundibulum becomes exceedingly small and unable to contain this great number of fibres.

Contrary to what might be expected from the study of sagittal sections, the transversal system of fibres is less clearly displayed in horizontal sections than in frontal ones. This is due to the fact that the ventral wall of the infundibulum is strongly invaginated. In the dorsal wall, the transversal system is very clear at proximal levels where it forms a commissure.

CHAPTER VI

I. THE ZONA PALISADICA

So far little attention has been paid to the structure of the "zona palisadica". In chapter III, it has been described as the peripheral zone of the infundibulum, being very poor in cells and rich in fibres of several kinds (ependyma, neuroglial, connective), of which, the ependyma fibres are the most conspicuous. In the following pages we want to summarize all the data on the topography, limits, and structure as concisely as possible in order to enable the reader to get an idea of the morphology of this zone. An accurate analysis of the structure of the nervous components of the zone will also be attempted. References to the zona palisadica are to be found in Herring ('08), Vázquez-López ('42), Benoit et Assenmacher ('51, '55), Bodian ('51), Nowakowski ('51), Wingstrand ('51), Knoche ('53), Hagen ('55) and Brettschneider ('56).

In order to be as clear as possible, we shall discuss the following items: 1., The histological aspect of the zona palisadica. 2., Its proximal limit. 3., The topography of the zone. 4., The course of the afferent nerve fibres to this zone.

1. THE HISTOLOGICAL ASPECT OF THE ZONA PALISADICA

Succesfully stained material is essential for the study of the zona palisadica. At their best the neurofibrillar techniques only partly succeed in disclosing the structure of this zone. From "fairly good" silver sections, little — if any — information can be obtained. Many aniline dyes leave it uncoloured. It is evident that a complete knowledge of the structure of this region may only be obtained by the succesful use of many different staining methods. This will give us a clear insight into the individual structural aspects and enable us to integrate these into a whole.

If we compare the zona palisadica in Bodian sections with the central zone of the infundibulum, we notice great differences. With low magnification, the zona palisadica appears as a layer of violet-reddish colour, poor in cells and of uniform optical density. At this magnification, no individual structural elements are discernible. The general colouring of this zone enable us to distin-

guish it from the corresponding central zone or, indeed, from the greater part of the nervous tissue. One may get the impression that this layer is of predominantly neuroglial nature, but a comparison with the genuine neuroglial lining of the base of the diencephalon and chiasm soon disproves this. The general colouring of these two structures is too different to be the same thing. In the third ventricle there is also a neuroglial layer interposed between the ependyma and the nuclueus ventrodorsalis of the tuber (the "glia interna" of Nowakowski). This zone also shows important staining differences when compared with the zona palisadica. If we want to find something in the nervous system resembling this zone in a Bodian section, we must look at the external layer of the cerebellar cortex (the plexiform or molecular layer) or to the first layer of the cerebral cortex (molecular layer of Cajal). Especially the plexiform layer of the cerebellum (in formaline fixation) strongly resembles the zona palisadica, i.e., in the general, more or less violet colour, in the scarcity of easily stainable structural elements (cells, fibres), in a variable degree of diffuse staining of the background and in the uniform optical density. It seems as if the silver is deposited on all structural elements of the zone almost without specificity.

Under powerful objectives, we notice that the diffuse staining of the background and the characteristics of the fibres are mainly responsible for the unusual aspect of this zone. In the zona fibrillaris, the fibres run grouped in bundles and the background remains completely unstained. A high degree of contrast is, therefore, obtained. The fibres of the zona palisadica run singly and their course is extremely irregular; often they seem to be immersed in a medium (the interfibrillar substance) which is stained various shades of reddish or violet. The contrast between clearly outlined elements and background diminishes because of this.

In the following analysis of the structure of the zona palisadica, special attention is paid to the nervous components of it. Other structural constituents such as neuroglia, connective tissue etc. requiring special methods of staining, will be mentioned in passing but not dealt with.

It is possible to divide the zona palisadica into two zones of somewhat different histological constitution. This distinction is based on the considerable differences in the vascular structure, which exist around the perimeter of the infundibulum. A glance at a transversal section of the infundibulum stained with azan is enough to reveal striking differences in the distribution of the blood vessels (fig. 23). These differences influence the structure of the nervous components which are supposed to be intimately related to the blood vessels. The capillary loops are most numerous in the ventral wall where they can be found in great numbers on either side of the median line. The dorsal wall also shows a number of capillary loops, but they are less numerous than in the ventral one. The lateral wall is characterized by the almost complete absence of blood vessels. In fact, the density of the vascularization of both the ventral and the dorsal wall

diminishes as we approach the lateral levels. Once we arrive at the lateral wall, we find practically no vessels.

The zona palisadica can be divided into: a) Areas rich in vessels and b) Areas poor in vessels. The zona palisadica of the ventral wall belongs to the former group; the dorsal wall, although less vascular, can also be reckoned to this group. The zona palisadica of the lateral wall is, however, almost completely avascular, thus belonging to the latter group.

Structure of the areas rich in vessels. The blood vessels play an important rôle in the structure of these areas. It is characteristic that they penetrate into the ventral wall of the infundibulum. The majority of them do not penetrate beyond the zona palisadica; they belong to the "short" type of Engelhardt ('56). Others penetrate into the zona fibrillaris — sometimes as far as the zona ependymalis. These belong to the "long" type of Engelhardt. The greater concentration of vessels in the ventral wall occurs on either side of the sulcus centralis proximalis infundibuli. In these places, the zona palisadica has its maximum thickness.

Practically all vessels in the ventral wall have a connective sheath, which can be stained blue with the anilin blue of the azan method. Surrounding this sheath, a perivascular space exists the structure of which gives this area its particular appearance (fig. 49). It can easily be seen that connective fibres from the

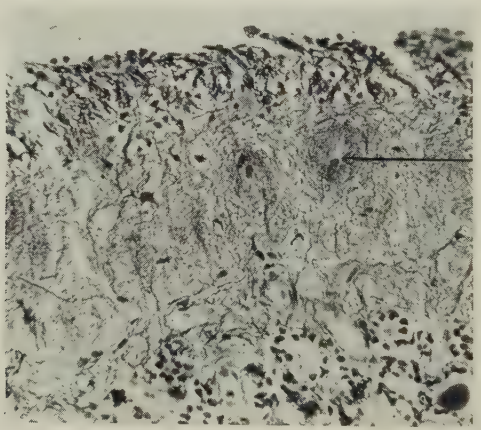


Fig. 49. Transversal section of the ventral wall. Two blood vessels in the zona palisadica are surrounded by a darkly-stained space (perivascular space). Bodian stain. Obj. 25. Oc. 8. Neg. 8776.

perivascular sheath of the "short" capillary loops connect each other as a system of bridges. These connective bridges form a continuous barrier which divides the zona palisadica into two subzones: one lies between the zona fibrilaris and this barrier and is the zona palisadica proper. The second lies between the barrier and the pars infundibularis, constituting what we call "zona granulosa", in accordance with Hanström ('53) and Hagen ('55) (see chapter V, p. 93).

The zona palisadica must be considered as the site of termination of the fibres of the tractus tubero-hypophyseus and possibly of some fibres of the tractus supraoptico-hypophyseus. In Gomori sections, the zona palisadica is stained light red; this contrasts strongly with the staining of the distal peripheral zone of the neurohypophysis which is stained blue. This important observation, and his – somewhat ungrounded – belief in the existence of nerve fibres in the zona palisadica, allowed Nowakowski ('51) to distinguish two separate hypothalamo-hypophyseal systems: 1. "The system of the tractus supraoptico-hypophyseus and the neural lobe" and 2. "The system of the tractus tubero-hypophyseus and the pars distalis" (for a detailed account of the present views of these authors see Spatz '58).

Nerve fibres in the zona palisadica were presumably seen by Cajal ('94) and by Herring ('08). The latter mistook them for ependyma fibres. The first clear and correct description of them was by Vázquez-López ('42), who drew attention to the existence and importance of the perivascular space in the infundibulum of the horse. Nowakowski ('51) described them as belonging to the tractus tubero-hypophyseus, but his pictures (figs 19 and 20 in his article) are unconvincing. The best pictures of the zona palisadica are those of Hagen ('55, '57).

The appearance of the zona palisadica is accompanied by the disorganization of the singly-running fibres of the tractus tubero-hypophyseus. These fibres soon lose their longitudinal course and become very irregularly disposed. They are partly involved in the innervation of the "short" type of capillary loops, i.e., those vessels which do not penetrate into the ventral wall beyond the zona palisadica. The innervation of these vessels represents an heterogeneous synapse, a connection between a nerve fibre and a non-nervous receptor (capillary). I think that a detailed knowledge of the structure of the perivascular space is essential for the understanding of the mode of this innervation, but we are still very far from this goal. The material now at my disposal permits me to produce the following data.

Every capillary loop of the infundibulum appears stained blue in azan sections. Several cell- nuclei either superimposed or bulging into the lumen, stained red are seen. These nuclei are often more or less round, and probably belong to the endothelial cells of the vessel's wall. It is worth remarking that in a great number of the capillary loops, very long cell-nuclei are found which look like smooth muscle cells. Around the walls of the vessels and in contact with them, there is a space of which the inner structure has defied our analysis. In azan sections, this space is stained red, and it is noticeably darker than in the neighbouring areas. In Bodian sections, this space is also impregnated; under the oil-immersion objective it appears as a mass with a colour somewhat similar to that exhibited by areas very rich in neuroglia fibres. Interspersed among this homogeneous, neuroglia-like space, are fragments of thin fibres which following all sorts of directions, seem to disintegrate into minute granula. In fig. 50, on

the contrary, no indication has been found as to the existence of this type of fibre. In any case, the number of nerve fibres, embedded in the neuroglia-like space is not great; where they are really very numerous is in another layer or space situated around the neuroglia-like one.

Summarizing we can say that the vessel wall is surrounded by a homogeneous, neuroglia-like space in which nerve fibres– possibly with degenerative characteristics – are submerged. In its turn this space is surrounded by a layer of fine, pale nerve fibres belonging to the tractus tubero-hypophyseus (fig. 50).

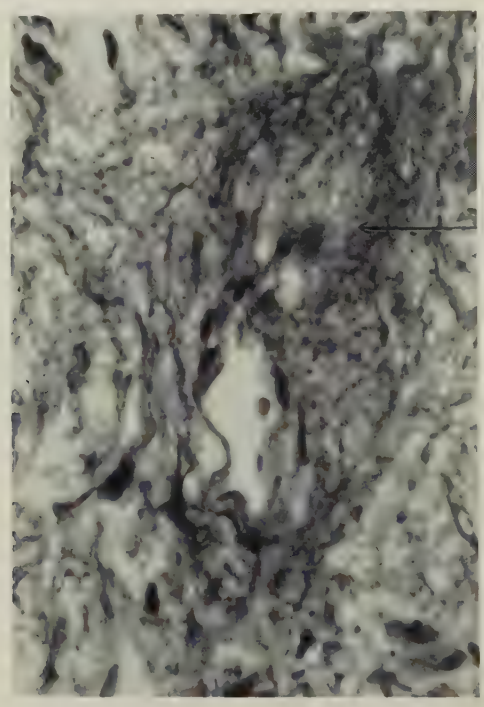


Fig. 50. Perivascular space at high magnification. Obj. 100. Oc. 8. Neg. 8822.

It shoud be mentioned that the perivascular spaces are practically devoid of cell-nuclei of any kind, at least in the zona palisadica. Nothing that could be compared to a Schwann's nucleus has been seen in our material. This supports the tuberal origin of the innervating fibres of the "short" capillary loops, and not the vegetative origin.

Many small veins of the mantle plexus are also profusely innervated. These vessels lie in the limit between pars infundibularis and zona palisadica. I have noticed that many of these vessels lack the neuroglia-like space. The delicate, coiled nerve fibres are very clear, being situated relatively closer to the vessel's wall. Sometimes the nerve fibres invade the pars infundibularis accompanied by the vessels, but they cannot be traced for long distances in the parenchyma. This is also true of the dorsal wall.

Particular nerve terminals, such as rings, endbulbs, Herring bodies or "endlamellae" have been found in the perivascular space. They occur more frequently around the basal capillaries than around the "short" capillary loops.

The "long" capillary loops, less numerous than the "short" ones, have quite a different mechanism of innervation from the latter. It must be remembered that every "long" vessel must be partly situated in the zona palisadica in order to reach the central zone of the infundibulum. The part of the vessel situated in the zona palisadica may or may not have a perivascular, neuroglia-like space. Usually they do. What is characteristic is that as soon as the vessels penetrate the central zone of the infundibulum, they completely lose the neuroglia-like perivascular space. In the central zone, the vessel is surrounded by the fibre-bundles of the tractus supraoptico-hypophyseus which seem pushed aside by the vessel. In frontal sections, the fibre bundles seem to have little to do with the innervation of these vessels.

We can confirm the findings of Brettschneider ('56) concerning the existence of more or less isolated fibres originating in the tractus supraoptico-hypophyseus (above all in those bundles situated close to the zona ependymalis) which – leaving their original course – cross the zona interna (central zone) to incorporate into the fibre plexus of the zona palisadica. These fibres are in general thicker than those of the tractus tubero-hypophyseus, or at least, they are more heavily impregnated by silver. In some cases we have seen one of these fibres approach a capillary (of the "long" type) in the central zone and run parallel to the vessel's wall for some distance. Nevertheless, this cannot be considered the rule in the innervation of the "long" capillary loops. Nerve terminals are distinctly present in the vascular areas of the zona palisadica: i.e., rings, endbulbs, "endlamellae" and Herring bodies. The relation of these nerve terminals to the blood vessels is not always clear. This is especially true of the "endlamellae". A detailed description of these terminals will be given in the following pages.

Structure of the avascular areas. These areas are represented by the zona palisadica of the lateral wall. This is specially developed at a level where the zona palisadica of the ventral wall has tapered out considerably. Although some vessels, above all of the "long" type of Engelhardt ('56), have been found, they are much rarer than in the ventral or in the dorsal wall. There are, therefore, few perivascular spaces in this lateral zone. The nervous elements in this zona are the following:

1. Nerve fibres. In good Bodian sections, the use of oil-immersion objectives reveals the existence of a great number of short fibre fragments in the zona palisadica of the lateral wall of the infundibulum. These fibres are very irregularly disposed: they are never grouped in bundles, thus contrasting with the central zone. The majority of the fibres are extremely thin and their impreg-

nation is pale. Nevertheless, although perhaps thinner than the axons of the central zone, the difference is not considerable. On the other hand, the axons of the central zone seem to be more intensely impregnated by silver than those of the zona palisadica (fasciculus tubero-hypophyseus).

A close study of this region reveals that the fibres run mainly in two directions. The first seems longitudinal, being perpendicular to the plane of sectioning (in transversal sections). These fibres are convoluted and twisted along their course. The second is more or less transversal, that is to say more or less parallel to the surface of the lateral wall in a transversal section. These fibres were sectioned under more favourable circumstances than the others, and can be examined for longer distances.

The possibility of mistaking ependyma fibres for nerve fibres can easily be ruled out. The ependyma fibres are very well-developed and clear in the lateral wall. They originate in the cells of the ependyma and fan out towards the outer basal membrane. This con easily be seen in azan sections. In successfully impregnated silver sections, not a trace of radial fibres is found in the lateral wall of the infundibulum; even in the outer basal mebrane, where often a slight notching – caused by the terminal arborization of the ependyma fibres – can be seen, nothing of this sort is present in the material selected for our description. Similarly, there is no question of mistaking connective fibres for nerve fibres in the lateral wall, owing to the scarcity of blood vessels. Furthermore, in series 213 and in many slides of series 1370, the connective sheath of the capillary loops of the infundibulum is completely unstained. The neuroglia fibres on the other hand are more difficult to eliminate. Although the method possesses a high specificity for nervous elements, some degree of staining of the neuroglia fibres is unavoidable. To elucidate this point, we have compared, in the same section, the structure of the glia externa lining of the base of the diencephalon (which is very rich in neuroglia fibres) with the zona palisadica of the lateral wall. The differences are enormous; in the former, the staining resembles an unspecific silver precipitate of minute grains, but no fibres can be recognized and the interstitial spaces are coloured dark violet. We believe that the majority of the darkly stained fibrillar elements in our series 213 and 1370 represent true nerve fibres.

The lateral area of the zona palisadica must be considered not only as a zone of transit for the thin, isolated fibres of the tractus tubero-hypophyseus, but also as the site of termination of a certain number of these fibres. This statement is supported by the finding of formations which can be interpreted as nerve terminals. These formations can be divided into three groups: 1. Rings. 2. End-bulbs. 3. Hypertrophied nerve fibres.

Rings. These formations are constituted by a closed ring with a diameter varying between 1–2 μ. They are predominant in the lateral part of the zona palisadica, but they can also be found in the dorsal and ventral wall. With an

oil-immersion objective we observe that they are more impregnated than the surrounding fibres of the tractus tubero-hypophyseus (fig. 51, 52).

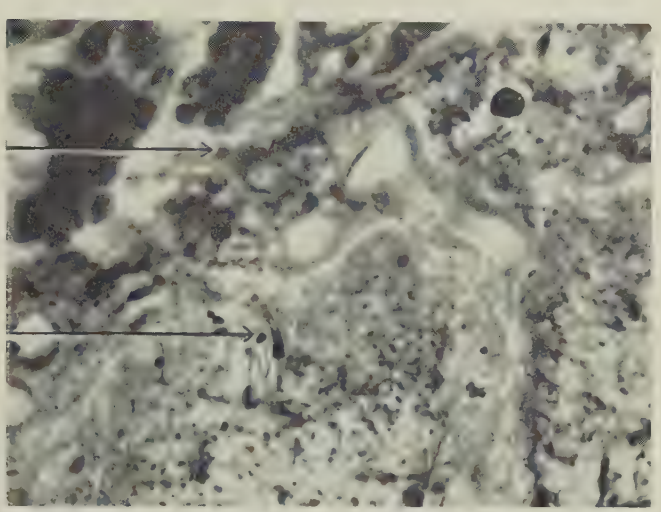


Fig. 51. Rings in contact with a blood vessel. Perivascular space. Dorsal wall of the infundibulum. Obj. 40. Oc. 8. Neg. 8305.

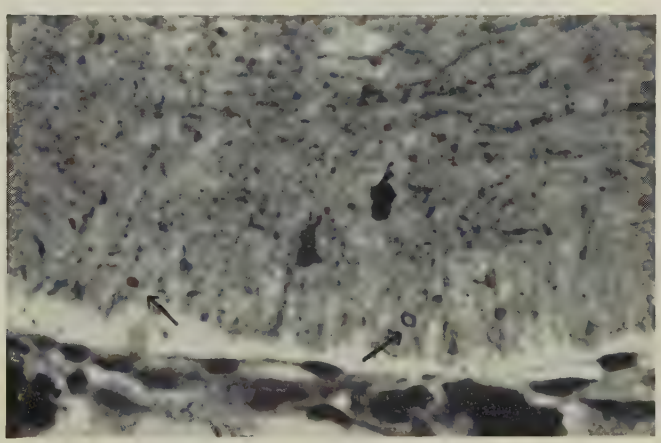


Fig. 52. Rings situated close to the borderline with the pars infundibularis. Obj. 40. Oc. 8. Neg. 8292.

The fibre which constitutes the ring is considerably thicker than the others; its curvature is fairly regular. These rings are not situated at a particular level in the zona palisadica; sometimes they can be found close to the pars infundibularis, but they may also be present in the borderline with the central zone.

The rings of the zona palisadica of the lateral wall are not situated around blood vessels or cells, but just scattered at different levels in the zona palisadica. It is difficult to tell which rôle these formations play in this area. The difficulty is that very often the rings appear isolated from any nerve fibre. It is evident

that the existence of a clear continuation between the rings and the nerve fibres is desirable, if we want to be sure that these rings are nerve terminals. Unfortunately, it seems that the majority of the rings cannot be shown to be continuous with genuine nerve fibres. We must add, however, that the staining characteristics of these rings are undistinguishable from the true nerve fibres.

In the dorsal wall, several rings have been seen in the immediate neighbourhood of the blood vessels (fig. 51), but the majority of the rings are situated in such a way as to make their relationship to the innervated elements obscure. Moreover, the rings situated with no obvious relation to any innervated elements, are constituted by relatively thick fibres, whereas those situated in perivascular spaces are constituted by fibres of approx. the same thicknes as those of the tractus tubero-hypophyseus.

Endbulbs. They are fewer in number than the rings. They are pear shaped,

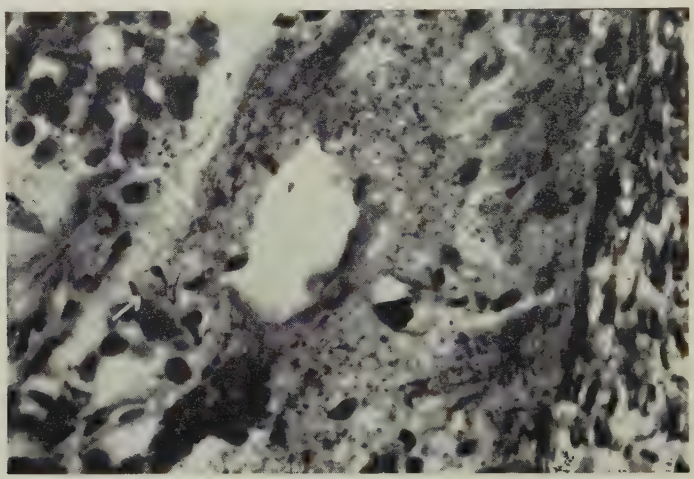


Fig. 53. Endbulb situated within the perivascular space. Obj. 25. Oc. 8. Neg. 8294.

showing their continuation with a nerve fibre clearly. The endbulbs are often situated in the neighbourhood of the blood vessels (fig. 53). They are much smaller than the Herring bodies and probably of a completely different signification.

Hypertrophied nerve terminals (Endlamellae). A third and very conspicuous element of the zona palisadica of the lateral wall consists of the tremendously enlarged terminal expansions of some nerve fibres. The neurofibrillar character of these formations is very distinct. They are formed by a very irregular mass of nervous substance disposed as a thin lamella with torn contours. The Bodian method stains these formations copper red, of approx. the same shade as that of the fibres of the central zone. They can be found not only in the zona palisadica of the lateral wall, but also in the central zone. Often they are situated close to the "short" capillary loops of the ventral wall but this must not

be considered the rule (fig. 54, 55, 56). In series 213, the nervous lamellae are stained dark-violet, in exactly the same way as the nerve fibres in this series. The differences in colour between these two series are certainly due to the use of two different brands of protargol.

The first and — as far as we know — the only description of these nervous formations in the neurohypophysis is Tello's ('12). His fig. 13 in particular is very striking; the lamellae are there represented perfectly and are called "mazas deshilachadas". He believed that these formations were regenerating fibres, which compensate for the continual degenerative phenomena which take place in the neurohypophysis.

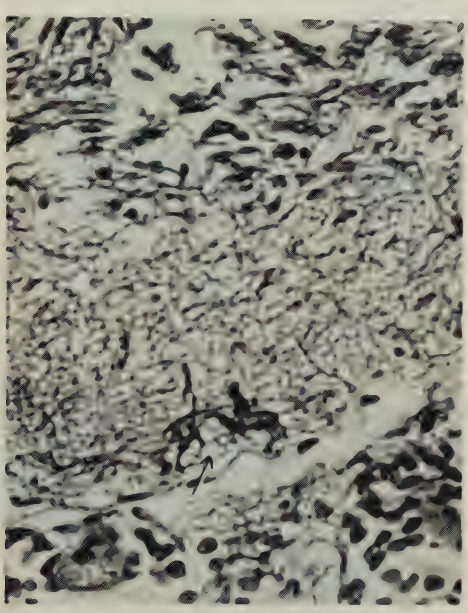


Fig. 54. Endlamella (degenerated nerve fibre?). Obj. 25. Oc. 8. Neg. 8761.

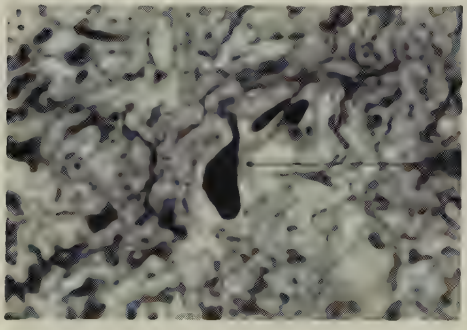


Fig. 55. Endlamella. Obj. 100. Oc. 8. Neg. 8820.

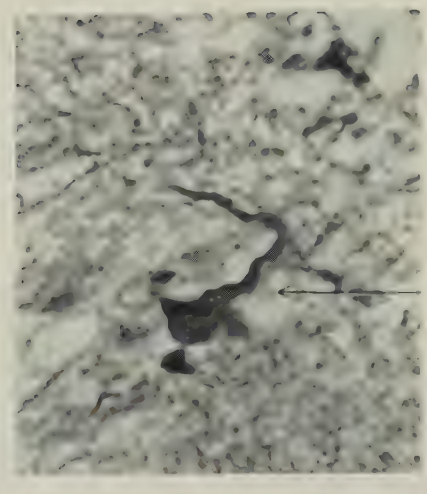


Fig. 56. Endlamella. Obj. 100. Oc. 8. Neg. 8821.

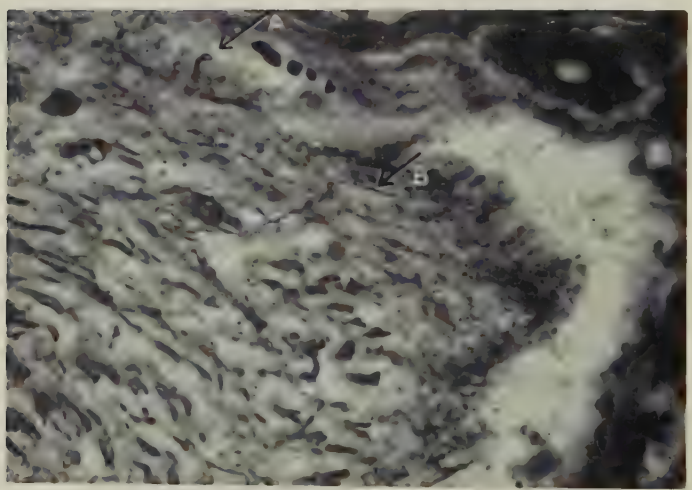


Fig. 57. Lateral wall of the infundibulum. A = Ring in connection with a nerve fibre. B = nerve fibre showing varicosities. Obj. 40. Oc. 8. Neg. 8311.

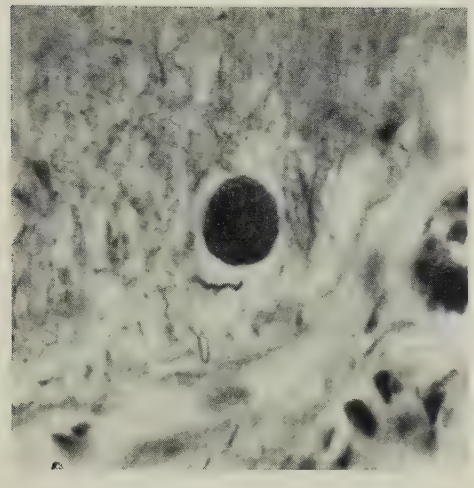


Fig. 58. Neurofibrillar „massue" probably representing a degenerating nerve fibre. Obj. 100. Oc. 8. Neg. 8527.

2. LIMITS OF THE ZONA PALISADICA

After this analysis of some aspects of the structure of the zona palisadica, we can ask ourselves what the limits of this zona are. The distal limit is easy to mark; we have said that the zona palisadica disappears when the pars intermedia (or the "nasale Umschlagzone") comes into contact with the infundibulum. The proximal limit of the zona palisadica is more difficult to establish; in order to do this we must first point out what the most essential structural characteristics of the zone are. The poverty in cells is undoubtedly a feature of the zone, but a negative one, and we prefer to look for something more positive. *The more or less diffuse staining of the interstitial spaces (background) and the rapid disorganization of the singly-running fibres of the tractus tubero-hypophyseus are essential for deciding what in Bodian material is zona palisadica and what is not.*

It can easily be seen that no zona palisadica is present in the ventral lip of the entrance area. Examining more distal sections, we observe that the fibres situated in the most peripheral position, i.e., in contact with the pars infundibularis, are not arranged in bundles, but run singly. These fibres are the continuation of the palisade system of the ventral lip and belong to the tractus tubero-hypophyseus. At this level, the zona palisadica has not yet appeared; this level corresponds to the beginning of the lateral lip of the entrance area. Slightly more distally, some fibres of the tractus tubero-hypophyseus (peripheral fibres) situated approx. in the median line begin to get surrounded by a diffusely impregnated mass, or, in other words, the interfibrillar spaces of these fibres (which were completely colourless so far) begin to show a diffuse impregnation. At this level, the zona palisadica begins. It should be noted that it appears in the median line of the ventral wall.

In more distal levels, the zona palisadica of the ventral wall becomes thicker and extends toward the lateral wall. In the lateral wall this particular zone soon appears and stops before reaching the lateral lip. At this level, the zona palisadica of the ventral wall has its maximum thickness; numerous capillary loops penetrate into the wall. It is interesting that in those very proximal levels of the ventral wall, where the zona palisadica has not yet appeared, no capillary loops exist.

We draw the conclusion that zona palisadica is not the same as the "periphere Zone" of Nowakowski. According to him, the cell-density is the essential criterion for distinguishing between central and peripheral zone of the infundibulum and hence, he declares that his "radix infundibuli" represents "periphere Zone": "Am caudalen Anteil fällt auf, dass der Kern von der Pars infunlibularis der Adenohypophyse (innerhalb der Sucus infundibularis) durch eine schmale zellfreie Zone geschieden wird. Diese Zone hat die Charaktere der peripheren Zone des Infundibulum". We do not concur with this statement; the "radix infundibuli" of Nowakowski represents the zona fibrillaris, and this is certainly not the same as the zona palisadica. In the "radix infundibuli", the zona palisadica has not yet appeared. This proves that the criterion of the poverty of cells is not adequate for determining the limits of the zona palisadica.

3. THE TOPOGRAPHY OF THE ZONA PALISADICA

Information on this point has been given in chapter IV. In the greater part of the infundibulum the zona palisadica is present. The zone appears for the first time in the median line of the ventral wall. From here it extends laterally and it increases its thickness. In the ventral wall, zona palisadica and pars infundibularis reach their maximum thickness in approx. the same level.

At more distal levels, the zona palisadica begins to decrease in the ventral wall and to increase in the lateral one, where it soon becomes thicker than in the ventral wall. It can be seen clearly that, in passing from the lateral to the dorsal wall, the zona palisadica gets progressively thinner until it disappears. The lateral lip, the dorsal lip and part of the corresponding walls have no zona palisadica.

The dorsal wall of the infundibulum has also no zona palisadica over a certain extension (fig. 23). At slightly more distal levels this zone appears in the dorsal wall, showing approx. the same characteristics as in the ventral one (fig. 22). Capillary loops are also present, but less frequently.

The insertion area of the infundibulum in the tuber cinereum has no zona palisadica in all its extension. This zone begins at more distal levels, never reaching up to the ventral, lateral or dorsal lip of the entrance area.

4. THE COURSE OF THE NERVE FIBRES TO THE ZONA PALISADICA

The course of the tractus tubero-hypophyseus as far as the entrance area has been described in chapter V. We have said that these fibres occupy a more

central (internal) position, i.e., they descend towards the entrance area close to the wall of the third ventricle. These fibres are not so clearly grouped in bundles and they are not concentrated into a densely arranged stream as the supraoptical fibres are. Once they have arrived at the entrance area, the tuberal fibres are situated in the n. infundibularis wedge zone, where they are not so conspicuous as the neighbouring supraoptical fibres. We shall now give an account of the further course of the tuberal fibres up to their termination area (the zona palisadica)

In the ventral lip we find what seems to be an exception to the rule that the tuberal fibres are always more internal (central) than the supraoptical ones. The superficially situated palisade system belongs to the tractus tubero-hypophyseus. The greater part of these fibres descend to this position at a level in which Gudden and Ganser commissures are still to be seen. This means that the palisade system is formed before the formation of the commissural system of the ventral lip. It must be acknowledged that some fibres of the tuber cross perpendicularly the commissural system to be incorporated into the palisade system. Collaterals of the commissural fibres also join the palisade group. At more distal levels we find these fibres running singly in the most peripheral part of the ventral wall. *The tuberal fibres of the ventral wall are in part, the continuation of the palisade system of the ventral lip.*

In the lateral lip the supraoptical fibres are disposed peripherally and the tuberal ones internally. This situation is soon reversed, so that both systems occupy their ultimate positions, i.e., the supraoptical fibres in the internal zone of the zona fibrillaris and the tuberal fibres in the external one, bordering on the pars infundibularis. *This reversal necessitates a crossing of the fibres of the two systems in order to bring it about.* This crossing of the fibres of both systems is very difficult to se (fig. 31). This is caused by several factors : firstly, it is difficult to see the palely impregnated tuberal fibres among the heavily stained bundles of the supraoptical system. Secondly, the angle of these crossings is very acute and hence the fibres of both systems run close to each other for some distance, which makes it difficult to distinguish these two systems. Thirdly, the crossings are not concentrated in one single place; they occur along some extension of the infundibular wall. All this adds to the difficulties of obtaining convincing photographs of it. Nevertheless, with oil-immersion lenses it can be observed that the pale-stained tuberal fibres cross the more heavily impregnated bundles to gather between the pars infundibularis and the zona fibrillaris of which they form part. The crossings can be observed more clearly in the junction of the lateral with the ventral wall.

The course of the nerve fibres entering the infundibulum through the dorsal lip seems to be most interesting and complicated. We have mentioned before that many fibres entering through the dorsal lip cross the median line to go to the opposite side. Thus, a decussation takes place. Diepen ('41) was the first (and hitherto the only) scientist who has mentioned a decussation of nerve

fibres in the proximal part of the dorsal wall. On p. 34 the says: "Near the infundibulum very thin but clearly myelinated fibres arise from the nucleus. They run caudoventrally into the sidewall of the hypophyseal stalk. Caudally they enter the hindwall of the hypophyseal stalk decussating with the fibres of the other side. Beyond the decussation I was not able to trace them further into the hypophysis". According to Diepen these fibres originate in the nucleus arcuatus (fig. 15 of his thesis). These observations were made on sheep.

We confirm the existence of decussating fibres in the dorsal lip. (fig. 36). The further course of the fibres is difficult to ascertain; the fibres seem to form the transversal system of the dorsal wall which terminates partly in the zona palisadica of the dorsal wall and partly, after turning in the lateral wall, in the zona palisadica of the ventral wall. Further observations on the course of the dorsal fibres are required to clarify this point.

II. OBSERVATIONS ON THE VASCULAR ARRANGEMENT OF THE NEURAL LOBE

The vascular supply of the cat hypophysis has often been studied in detail. The most important references to this subject are to be found in Herring ('08), Wislocki ('37), Morato ('39), Morin ('41), Merényi ('48), Nowakowski ('51), Engelhardt ('56), and Duvernoy ('58). Although this thesis is not immediately concerned with the vascular disposition of the hypophysis, we want to draw attention to a particular disposition of the blood vessels of the neural lobe, not described hitherto. These observations have been made not only on my own material, but also on that of the Max Planck Institute of Giessen.*

As is well-known, the ventral wall of the infundibulum of the cat (and the dorsal one also to a smaller degree) are pierced by numerous blood vessels which originate in the "mantle-plexus", that is to say, in a system of vessels lying between the pars infundibularis and the infundibular wall. These vessels penetrate into the wall of the infundibulum; according to the degree of this penetration they can be divided into "short" and "long" (Green and Harris '46; Engelhardt '56). According to the latter, the penetrating vessels (capillary loops, Spezialgefässe) are to be found not only in that part of the infundibulum which is lined by the pars infundibularis, but also in what he calls "Zwischenstück", i.e., in the narrowest part of the infundibulum, where they are shorter than in more proximal levels.

Of the neural lobe he says the following (p. 143): "Rechts vom Pfeil geht das Zwischenstück in den ebenfalls an den Recessus angrenzenden Hilus des Hinterlappens über, der durch gröbere, unregelmässige Schlingen angioarchitektonisch gekennzeichnet ist". The figures 5a and 6 of his paper do not leave any

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* In this connection I should like to thank Prof. Spatz and Dr. Diepen, who have been so kind as to let me study the extensive material of this institute.

doubt as to the existence of two angioarchitectonic different territories in the neural lobe; one corresponds with what he calls "Hilus" which is the proximal part of what I have called "central zone of the neural lobe". As his figs 4, 5a and 6 show clearly, the vascular disposition of the proximal part of the central zone of the neural lobe is the same as that of the infundibulum. This vascular architecture supports our division of the neurohypophysis into a central zone and a peripheral zone (see chapter IV). The vessels in the peripheral zone of the neural lobe are disposed in a net of capillaries strongly developed in the borderline with the pars intermedia.

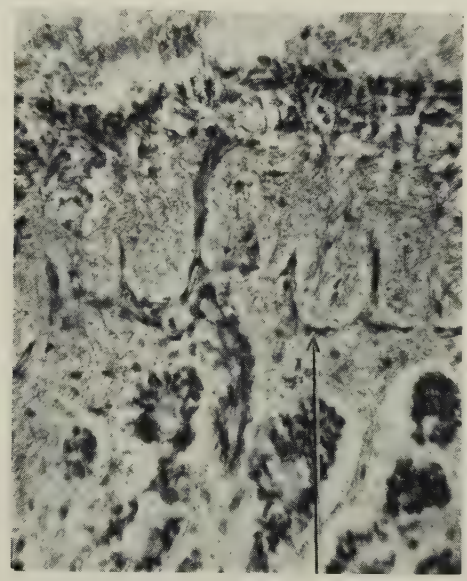

Fig. 59. Transversal section of the ventral wall of the infundibulum showing the capillary loops. Obj. 20. Oc. 8. Neg. 6941.

The infundibular-like disposition of the vessels in the proximal part of the central zone of the neural lobe of the cat has long been known. In 1946, Green and Harris reported: "A sharp distinction is thus visible between that part of the neurohypophysis which surrounds the infundibular recess and the remainder of the neural lobe, on the basis of their vascular pattern". Similarly, Merényi (1948), speaking of the "mantle-plexus" lying between the neurohypophysis and the pars infundibularis (or intermedia) says: "... Er liegt wie bereits oben erwähnt, nicht nur auf der Oberfläche des Stiels, sondern man kann ihn von der oberen Grenze der Hypophyse bis zu der Mitte des Hinterlappens verfolgen" (see his figs 4 and 8). Duvernoy (1958) has also noted this disposition in the proximal part of the neural lobe: "... En effet, sur des coupes frontales et sagittales, intéressant le lobe postérieur, le réseau primaire est d'abord nettement

individualisé, séparant la substance infundibulaire du tissu du lobe nerveux. Mais plus nous nous déplaçons vers l'arrière, plus cette disposition devient imprécise; le réseau capillaire se continue sans démarcation visible avec les vaisseaux du lobe postérieur; les anses capillaires persistent toujours mais leurs origines se trouvent à des niveaux variables; certaines naissant profondément n'atteignent l'infundibulum qu'après un long trajet vertical" (p. 81).

Our own observations on the neural lobe of young cats (fig. 25) strongly support these views. Here the "mantle-plexus" clearly separates the prolongation of the ventral wall of the infundibulum from the peripheral zone of the neural lobe. Examining more distal sections, we see that this sort of barrier interposed between these two structurally different areas is broken in several places, owing to the fan-like spreading of the nerve fibres of the infundibulum into the peripheral zone of the neural lobe. In this series, the "mantle-plexus" seems disrupted at a certain (distal) level. This is in complete agreement with the above-mentioned descriptions.

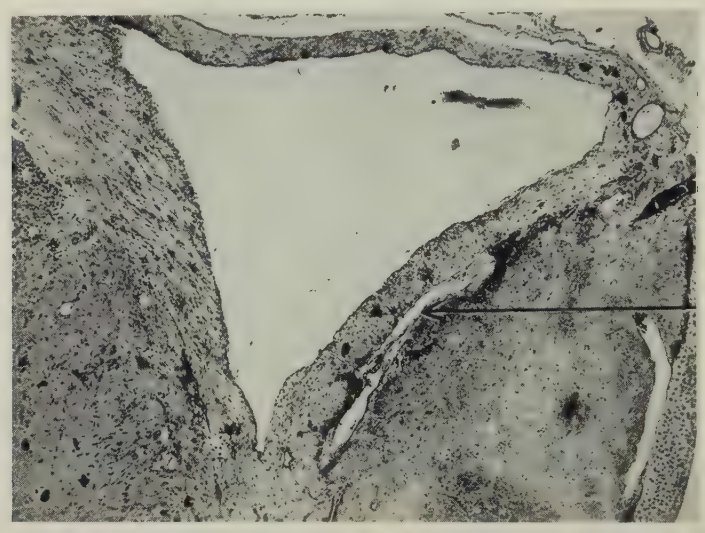

Fig. 60. Sagittal section showing the neural lobe. Note vessel branching out upwards towards the lumen of the recessus infundibularis. This section belongs to the collection of the Max-Planck Intitut of Giessen. 70x.

We have mentioned that there are literature data concerning a prolongation of the "mantle-plexus" as far as the proximal part of the neural lobe. The significance of the change of position of this plexus should not be underestimated; in the proximal hypophysis, this system of vessels is situated between neurohypophysis and adenohypophysis, whereas in the distal (intrasellar) hypophysis, the "mantle-plexus" is situated between central and peripheral zones of the neurohypophysis, having lost its connection with the adenohypophysis.

In the material of prof. Spatz of the Max Planck Institute of Giessen I have

observed that the distinction between the two angioarchitectonic different regions is not only possible in the proximal part of the neural lobe but holds good for the whole neural lobe, so also to its distal part. As fig. 59 (Katze E29, sagitt. section n. 185, Gomori) demonstrates, a thick vessel, exactly in the limit between central and peripheral zones, gives four branches; each of these ramify into groups of three. Some of these branches reach as far as the neighbourhood of the zona ependymalis of the central zone of the neural lobe. On top of these ramifications, accumulations of Gomori positive material are seen. This figure and those of Engelhardt and Duvernoy (photo 18) demonstrate the infundibular-like disposition of the blood vessels along the central zone of the neural lobe over the whole extension. It is evident that the thick vessel represented in fig. 60 belongs to the inferior hypophyseal artery system; I am inclined to believe that this vessel is one of the main branches of the inferior hypophyseal artery. It is very likely that this vessel anastomoses with the "mantle-plexus" system either by capillaries or by larger vessels. This is a point worth investigating in some detail; anastomoses of arteriole caliber would influence the direction of the blood-flow in the "mantle-plexus" system since the blood in this relatively large artery is much closer to the general circulation than that of the primary capillary net. These problems need further study.

DISCUSSION.

The hypophysis is an organ with a great variability in the degree of development of the different parts which constitute it. It is not necessary to look for very distant species to have this confirmed, but within the very group of the mammals, the constitutive differences of the hypophysis are great. The pars intermedia is lacking in whales; the pars infundibularis is absent in the anteaters and armadillos and in some of these animals, both pars infundibularis and pars intermedia may even be absent (Herlant '58).

While studying the hypophysis of young and adult cats, we were struck by the considerable differences from specimen to specimen. These differences are responsible for the fact that the descriptions of scientists do not always correspond. We think that the points which are most likely to need discussion are the following: 1. The extent of the pars intermedia lining of the dorsal wall. 2. The transition zone between pars distalis and intermedia. 3. The relation between the pars infundibularis and the pars intermedia. 4. The form of the infundibulum in a cross-section at a level corresponding with the debouchment of the infundibulum in the neural lobe. These points require some attention.

Fig 180a of Romeis ('40) is typical of the way in which a median sagittal section of the hypophysis is most frequently represented. Practically the whole extension of the dorsal wall of the neurohypophysis is illustrated as being without lining of pars intermedia. Most of the series of our material show, however, a clear and sometimes relatively thick layer of pars intermedia covering a large extent of the dorsal wall (fig. 8). According to this fig., the dorsal wall is naked only for a short extension, viz., between the end of the lining of the pars infundibularis and the beginning of the pars intermedia, and also at the distal pole of the gland (where the inferior hypophyseal arteries enter the neural lobe), which is almost rudimentary. Two series of our material belonging to young cats are in accordance with the schema of Romeis. Thus age seems of importance in accounting for these variations, but it is probably not the only factor. In any case very considerable individual variations are likely to occur here.

The transition between pars distalis and pars intermedia is also different according to the age of the animal studied. We concur with the description of Romeis ('40, p. 280-281). Here again the fusion of the thin lamina of pars distalis, which accompanies the pars intermedia towards the distal pole of the neural lobe, may soon take place or may be delayed until it reaches the vicinity of the dorsal pole of the neural lobe.

The relation between pars infundibularis and pars intermedia is a much discussed matter. On p. 264 Tilney ('13) states that his pars infundibularis (our pars intermedia) "fuses with the pars tuberalis without any sharp line of demarcation". Strangely enough, this statement is not in agreement with his own fig. 1 in which a wide space, occupied by the pars distalis, separates the end of the pars infundibularis from the beginning of the pars intermedia. According to Romeis (fig. 180a), the pars infundibularis and the pars intermedia are separated from each other by a wide extension of glandular tissue which shows a different structure from either pars distalis or pars intermedia. I subscribe to this view with this reservation, viz., that pars infundibularis tissue wedges itself between this somewhat modified zone of the pars distalis and the wall of the infundibulum over a certain extension (fig. 27).

The narrowest part of the infundibulum, i.e., that part which we have compared to the neck of a sand-glass, shows very different shapes in cross-sections. The two extremes are the three pointed star (fig. 14), and the trapezoid shape. Between these two extremes, all sorts of transitional shapes are possible.

Many authors have acknowledged that two zones can be distinguished in the proximal part of the neural lobe (Green and Harris, Merényi, Rumbaur, Nowakowski, Engelhardt, Duvernoy). The study of the disposition of the blood vessels in the neural lobe has helped a great deal in making this distinction. Nevertheless, with the exception of Rumbaur, the other authors have not realized that the zona interna of the processus infundibularis is but the prolongation of the internal zone of the infundibulum, nor that it encloses the terminal expansion of the recessus infundibularis in all its extension. The importance of this disposition as a basis of a more logical division of the whole neurohypophysis has been overlooked also, even by Rumbaur, whose fig. 1 gives a correct picture of the situation in a parasagittal section.

I want to discuss here the division of the neurohypophysis given by Nowakowski ('51) which being in agreement with that of Rioch, Wislocki and O'Leary ('40) is the more widely accepted to-day. Nowakowski divides the neurohypophysis of the cat into three regions. These are: 1. The infundibulum. 2. The intermediary portion (Zwischenstück). 3. The neural lobe (Hinterlappen). According to him the infundibulum is the most proximal part of the neurohypophysis being lined up by the pars infundibularis. This proximal part is constituted by two layers, the zona interna and the zona externa.

The intermediary portion (Zwischenstück), forms the link between the infundibulum proper and the processus infundibularis. It presents differences both in structure and in topographical relation with the adenohypophysis which permit us to distinguish it from the infundibulum. These differences are: 1. The disappearance of the zona externa. 2. The substitution of the pars intermedia for the pars infundibularis.

The neural lobe is that part in which two zones can be observed, a central

one rich in fibres and a peripheral one rich in blood vessels where light and dark areas are placed with a certain regularity. The neural lobe is also characterized by the fact that it is surrounded exclusively by the pars intermedia.

This division of Nowakowski is based upon two criteria: a) the existence of regional variations in structure (for example the presence or absence of the zona externa of the infundibulum) and b) the extension of the lining of the different parts of the adenohypophysis with which the infundibulum comes into contact. In spite of the apparently well-grounded and clear reasons for proposing such a division, we believe that some objections can be raised against it (Martinez, '58). In the first place, I think that the criteria employed by Nowakowski for establishing the division have been based exclusively on the study of the ventral wall of the neurohypophysis. The dorsal wall of what he calls infundibulum is only constituted by his "zentrale Zone". No zona palisadica is present at this level. In the "Zwischenstück" on the contrary, the dorsal wall is constituted by the "zentrale Zone" and the "periphere Zone", whereas the ventral wall is only formed by the "zentrale Zone". He has, furthermore, not seen that the dorsal wall of the infundibulum extends as far as the dorsal pole of the neural lobe, nor has he acknowledged the infundibular character of the whole central zone of the neural lobe. A division based exclusively on the situation in the ventral wall cannot be applied to the whole neurohypophysis. I believe that a division of the cat-neurohypophysis into three parts is untenable. Since the structure of the dorsal wall must also be taken into consideration, we think that our division into two parts, the zona externa and the zona interna is more in agreement with the facts.

The question whether this division can be applied to forms other than the cat, above all those with a shallow recessus is being studied now. Preliminary examination in the rat and cavia do not seem to contradict it, since the solid infundibular stem may be considered as originally hollow, of which the walls had secondarily fused, this causing the zona fibrillaris to take a central position, being surrounded by the zona palisadica. This needs further study, however.

A second question closely related with the preceeding one is our conjecture that the internal zone of the neurohypophysis may represent the wall of the primitive infundibular diverticulum. This appears in hematoxylin material as a wall of uniform structure, at least up to stadia of 30-35 mm. Until this time, the neurohypophysis consists of a wall constituted of an epithelial matrix with a low mitotic activity, which gives rise to ependymal and neuroglia cells. It is thus, essentially a cellular formation. Later (no data are available as to the moment of entrance of the hypothalamic axons in the neurohypophysis), the hypothalamic axons appear in the neurohypophysis in such great numbers, that they outnumber the cells, giving the impression that the neurohypophysis is a predominantly fibrillar organ. In the infundibulum, the cells remain close to the lumen of the recessus.

Still later, the neurohypophyseal wall begins to show a differentiation between the structure just described and a new layer, the external zone, characterized by its richness in vessels. We think that the external zone (zona palisadica and Herring's light and dark areas of the neural lobe) is a secondary differentiation of the wall of the primitive infundibular diverticulum, appearing not earlier than the stage of 40-50 mm crown-rump length. In this sense thus, the central zone of the neurohypophysis may be considered the more primordial of the two.

The blood vessels undoubtedly play an important rôle in the forming of the external zone. This is especially certain of the neural lobe which in the cat is constituted by considerable numbers of what Bodian calls the "inverted lobule"; the blood vessels being the architectural center of them. The lobular organization of the peripheral zone of the neural lobe, so clearly demonstrated by Bodian ('51) especially for the Opossum, may justify the use of the name "zona lobularis" to designate it. On the other hand, in the zona palisadica, the importance of the blood vessels in the constitution of the structure of the zone is less evident; there are zones where the vessels are as important as in the neural lobe (the zona palisadica of the ventral wall), but there are also zones where the zona palisadica is very well-developed and yet the blood vessels are lacking or, at least, very rare. This seems to demonstrate that a well-developed zona palisadica is possible in absence of vessels. That this zone is also possible in absence of the pars infundibularis was already shown by Herlant ('58).

It may be of some importance to stress that the adult neural lobe is the product of the differentiation of the distal part of the ventral wall of the primitive infundibular diverticulum. The dorsal wall does not take part in the forming of the neural lobe as we can observe easily in transversal sections in which the roof of the neural lobe is formed by the prolongation of the internal zone of the infundibulum. In fact, the lateral parts of the peripheral zone of the neural lobe may invest the dorsal wall to such an extent that only in the median plane the roof of the neural lobe is exclusively constituted by the internal zone of the infundibulum. We can arrive at the conclusion that the ventral and the dorsal wall of the primitive infundibular diverticulum are not equal in their potentialities; indeed, the potency to form the peripheral zone of the neural lobe (zona lobularis) does not exist in the dorsal wall. In this respect, the opinion of Tilney and others that the dorsal wall of the neurohypophysis may represent the "saccus vasculosus" of fishes may be remembered.

In chapter V, we have described a commissural system of fibres in the ventral lip of the entrance area. We should like to emphasize that this commissural system has nothing to do with either the Meynert or Ganser commissures. The former is placed more rostrally, in fact, it appears immediately behind the optic chiasm. Furthermore, this commissure is formed by myelinated fibres following a regular course, whereas our commissure appears more dorsally, at a level where the Meynert commissure is not present any more, and is consti-

tuted by unmyelinated fibres. At this level, the pars infundibularis of the adenohypophysis is already in contact with the floor of the third ventricle. We are thus, inside the ventral lip of the entrance area, i.e., at the level of the "radix infundibuli" of Nowakowski. As far as we know, this commissural system of fibres has not yet been described in the cat.

Laruelle ('34) describes the tractus supraoptico-hypophyseus as partially homo- and partially heterolateral in man. In the same way, the tractus paraventriculo-hypophyseus of Laruelle is made up of two main bundles (descending to the hypophysis) of which the fibres merge and cross the median line. This tractus, situated more internally than the former, is therefore completely heterolateral. The tractus hypothalamo-hypophyseus of Laruelle (which represents our tractus tubero-hypophyseus) is, on the other hand, homolateral. We have found that the last mentioned tractus also crosses the mid-line, at least in part. Except for this, we are in agreement with the description of Laruelle. In the cat, the commissural system of the ventral lip is constituted by supraoptical, paraventricular and probably tuberal fibres.

Commissural fibres are also present in the dorsal lip. It is difficult to determine the origin of these fibres, but it seems that they partially originate in the nucleus hypothalamicus posterior and the lateral hypothalamic area. The majority of these fibres cross the median line, going into the opposite side of the dorsal wall.

Fisher, Ingram, Hannet and Ranson ('34, '35, '38) first systematized the hypothalamic innervation of the neurohypophysis of the cat. These authors make a sharp distinction between the tractus supraoptico-hypophyseus which, according to them, is constituted by large number of relatively thick fibres situated in the ventral wall of the infundibulum, and the tractus tubero-hypophyseus which is constituted by thinner fibres and is situated in the dorsal wall. The majority of the fibres of both systems reach the neural lobe where they terminate. There is also a physiological difference between these two systems, because lesions of the tractus tubero-hypophyseus do not result in diabetes insipidus.

Spatz and his co-operators (Nowakowski, Diepen, Christ, Engelhardt) have very interesting views on the systematization of the hypothalamic innervation of the neurohypophysis. Two different systems of fibres are distinguished by them, not only by the different morphological properties of the fibres, but mainly by the stainability of the fibres with the Gomori method. These systems are: 1. The system of the tractus supraoptico-hypophyseus and the neural lobe. 2. The system of the tractus tubero-hypophyseus and the adenohypophysis. The first system originates in the nucleus supraopticus and paraventricularis. Their "thick axons" run in the central zone of the infundibulum and terminate in the neural lobe. With respect to the Gomori method, this system is Gomori positive.

The second system of Spatz originates in the nuclei of the tuber cinereum,

above all in the nucleus infundibularis. Most of these fibres terminate in the infundibulum, i.e., they do not reach the neural lobe.

According to Wingstrand ('51) the tuberal fibres cross the supraoptical ones (his observations were based on birds).

Nowakowski ('51) has shown that the external zone of the infundibulum is Gomori negative. He claimed that this zone, when stained with the Bodian method, reveals a dense plexus constituted by extremely thin nerve fibres. His illustrations to prove this point are unconvincing. These observations led him to postulate the existence of two different hypothalamic fibre systems in the neurohypophysis. This distinction is based on the results of the Gomori method. Since this method is incapable of staining the Gomori negative fibres, it cannot give any information concerning the origin, course and arrangement of the tuberal fibres. In fact, Spatz himself declares in his most recent paper ('58 p. 66): "Der Verlauf der feinen Fasern, die man unter der Bezeichnung Tractus tubero-hypophyseus zusammenfassen kann, ist sehr viel schwieriger zu verfolgen als der Verlauf der kräftigen und parallel angeordneten Fasern des Tractus supraoptico-hypophyseus. Hier bestehen noch viele Unklarheiten. Es ist möglich, dass sich in diesem Tractus auch Fasern von verschiedener Funktion zusammenfinden".

We hope that our paper helps to clarify the topography of the fibre systems concerned with the innervation of the neurohypophysis. We have also distinguished two systems of fibres in our Bodian material. These are: 1. The supraoptical system. 2. The tuberal system. The fibres of the former originate in the cells of the nucleus supraopticus, paraventricularis, and possibly in other regions situated at a more or less large distance from the hypophysis (some fibres may come from the fornix, and also from the H_1 field of Forel and the median forebrain bundle).

The origin of the fibres constituting the tubero-hypophyseal system is difficult to determine. The neurofibrillar methods generally used are inadequate in solving this problem. The cytoplasm of the small tuberal cells is poorly stained, often not at all; the staining of the "initial segment of the axon" is not satisfactory. These shortcomings and the use of thin sections (otherwise the pictures become difficult to interpretate owing to the superposition of large numbers of stained elements in the section) account for the fact that the problem of the connections between the tuber cinereum and the neurohypophysis has remained unsolved. We have said that the tuberal fibres originate in the nucleus infundibularis, ventromedialis, ventrodorsalis, paraventricularis, and area hypothalamica periventricularis posterior. Actually, we have seen some fibres issued from these nuclei descend towards the entrance area of the infundibulum where they join the maze of fibres in the nucleus infundibularis wedge zone, i.e., always in a position more internal than that of the supraoptical fibres. Only a small number of tuberal fibres could be traced to their nuclei of origin with certainty and this is by no means an easy task. We think that a great deal of work can still be

done on the tuber cinereum of the cat; not enough is known of the different cellular types and the fibre connections between the tuberal nuclei.

Tractus supraoptico-hypophyseus

The fibres of this tractus are grouped in the vicinity of the entrance area forming group 3 of figs. 28 and 31. The most rostral fibres of the tractus form the commissural system of the ventral lip. Whether these commissural fibres connect both supraoptic nuclei or pass into the contralateral side of the infundibulum has not been ascertained. The commissural system of the ventral lip is separated from the pars infundibularis by the palisade system of fibres which belongs to the tractus tubero-hypophyseus.

By far the greater part of the supraoptical fibres enter the infundibulum through the lateral lip of the entrance area. They are situated very superficially; in these proximal levels, no zona palisadica separates the supraoptical fibres from the pars infundibularis. If we follow them on their way towards the neural lobe, we see that they are first situated in the lateral wall of the infundibulum, forming the zona fibrillaris, which at this proximal level is separated from the zona ependymalis by the nucleus infundibularis wedge zone. Shortly afterwards, the fibres leave the lateral wall to enter the ventral one. Here they are still separated from the ependyma by the same wedge zone which soon disappears. At this moment, the supraoptical fibres (zona fibrillaris) make contact with the ependyma. In this way, an important topographical change occurs: the supraoptical fibres which in the entrance area were situated in the periphery, i.e., limiting with the pars infundibularis, attain a central position at a slightly more distal level. Because of this, they lose contact with the pars infundibularis and they come into contact with the ependyma. From this level onwards, the supraoptical fibres preserve this situation, i.e., they constitute the central zone of the infundibulum, until they pass into the light areas (Zwischenstreifen of Romeis) of the neural lobe.

Supraoptical fibres can thus be found not only in the ventral wall of the infundibulum but also in the lateral and dorsal wall. In the proximal part of the dorsal wall, the supraoptical fibres are found in areas somewhat away from the mid-line. Here, tuberal fibres are much more numerous. At more distal levels, owing to the somewhat helicoidal course of the nerve fibres in the infundibulum, supraoptical fibres can also be found in the median sagittal part of the dorsal wall.

The majority of the supraoptical fibres terminate in the dark areas (Verdichtungszonen of Romeis) of the neural lobe. A number of them do not reach it and terminate in more proximal levels. Some fibres seem to be concerned with the innervation of the ependyma; others terminate in the central zone showing either terminal swellings (Herring bodies) or disintegrating in minute granula. In our

material, Herring bodies are numerous in formalin-fixed series. Our alcohol-fixed material is, however, completely free from these formations.

Tractus tubero-hypophyseus

These fibres (very numerous) have attracted attention in the last years. They are more internally situated than the supraoptical ones, that is to say, closer to the third ventricle.

In a transversal section of the ventral lip (see schema 28), group 1 and part of 2 are constituted by tuberal fibres. Group 1 is the periventricular system, constituted by fibres originating in several nuclei (see p. 81). Group 2, called perifornical system, is constituted by supraoptical and tuberal fibres. The tuberal part of this bundle is represented by the axons of the nucleus ventromedialis and infundibularis. These axons join the other fibres of group 2, which originate from areas situated far away.

The tuberal fibres follow a more irregular course than the supraoptical ones and are less conspicuous because they are a shade lighter. We may say that these fibres converge towards the ventral lip to enter the infundibulum. There the tuberal fibres can be found: 1. In the nucleus infundibularis wedge zone. 2. In the commissural system, where they are obscured by the more darkly stained supraoptical fibres. 3. In the palisade system of fibres, situated between the pars infundibularis and the commissural system.

At more distal levels, the commissural system disappears. The zona fibrillaris of the ventral wall is constituted by very numerous fibres arranged in bundles which are the continuation of the commissural fibres and also of the bundles entering the ventral wall through the lateral one. The fibres which are situated close to the pars infundibularis can be distinguished from the rest, because they are not arranged in bundles and their staining is somewhat different from that of the more central fibres. The singly running fibres are the continuation of the palisade system of fibres, and they, therefore, belong to the tractus tubero-hypophyseus. At this proximal level, it is already possible to distinguish between both great fibre systems innervating the neurohypophysis. The tractus tubero-hypophyseus here occupies a position, which the zona palisadica occupies at more distal levels. The appearance of this zone takes place slowly. Little by little the interfibrillar spaces of the most superficial part of the zona fibrillaris – i.e., the part occupied by the tractus tubero-hypophyseus – become stained, thus contrasting with the remainder of the zona fibrillaris, which is characterized by a sharp contrast between the colourless background and the reddish-violet nerve fibres. The staining of the interfibrillar spaces and the sudden disruption of the longitudinal course of the fibres mark the appearance of the zona palisadica. *This zone is to be considered as the termination area of the fibres of the tractus tubero-hypophyseus.*

The disposition of the hypothalamic fibres entering the lateral lip of the en-

trance area is the following: two main systems can be seen in this region (fig. 31). The internal one descends towards the ventral lip close to the wall of the third ventricle. It represents group 1 (periventricular system) of fig. 28. On entering the ventral lip, these fibres are situated in the nucleus infundibularis wedge zone. The supraoptical fibres are situated laterally; they are in contact with the pars infundibularis. Presently these two systems interchange their respective positions; the tuberal fibres of the periventricular system which were placed centrally, i.e., close to the lumen of the third ventricle, gradually attain a more peripheral position, until they become arranged in the contact zone of the infundibulum with the pars infundibularis. Conversely, the supraoptical fibres which occupied in the lateral lip a peripheral situation, become progressively more central and at last make contact with the ependyma. *This means that the fibres of the two hypothalamic tracts cross each other in order to be able to obtain their ultimate positions* (fig. 31).

The morphological criteria which enable us to distinguish the fibres belonging to either of these systems have repeatedly been exposed. Once the fibres of the supraoptical system have arrived at the entrance area of the infundibulum, they are grouped in bundles of between 4-16 fibres. Their course is always more regular than that of the tubero-hypophyseal fibres. There is also a staining difference among these axons: the former are stained reddish by the Bodian method, whereas the latter are usually lighter.

The two hypothalamic systems innervating the neurohypophysis are morphologically not completely independent from each other. Many fibres from the tuber descend to the ventral lip together with group 2. The commissural system of the zona externa of the ventral lip also contains many fibres belonging to the tractus tubero-hypophyseus. Furthermore, tuberal fibres are present in the central zone of the infundibulum, where they are obscured by the great number of heavily stained supraoptical bundles.

The disposition of the fibres in the dorsal wall is the following: in median sagittal sections there is a system of fibres situated in the peripheral part of the pars caudalis tuberis which penetrates into the most peripheral part of the dorsal wall (fig. 47). This system can be traced into the pars caudalis tuberis up to a certain level, where it disappears rather abruptly. Under high magnification, it can be observed that these fibres become transversal. The axons of the nerve cells of the nucleus infundibularis (pars posterior) contribute to the formation of this bundle. In transversal sections it can be seen that this peripheral system of fibres originates – at least in part – in the lateral hypothalamic area and in the nucleus hypothalamicus posterior. There are also fibres which run parallel to the wall of the third ventricle entering the dorsal lip. This purely dorsal system of tuberal fibres is not single but paired; it is worth remarking that both fibre groups (i.e., the right and the left) interchange many fibres which – crossing the mid-line – pass to the contralateral side. A considerable number of commissural

fibres is thus present in the dorsal lip. These fibres are situated almost in a transversal plane; they can be followed into the dorsal wall in the zone close to the ependyma. where they contribute to the formation of the transversal system of fibres of the dorsal wall. In fig. (48) the fibres of the dorsal wall are very clearly disposed into two strata: one, peripheral, is the continuation of the sagittal system of the pars caudalis tuberis; the other, central, transversally cut, is the continuation of the commissural fibres of the dorsal lip.

The tuberal fibres which have entered the dorsal lip of the infundibulum terminate either in the zona palisadica of the dorsal wall, or they pass into the lateral wall of the infundibulum where they may end, or – continuing their way – they may reach the zona palisadica of the ventral wall. This is supported by the great number of transversal fibres present in the dorsal wall.

The question whether the majority of the supraoptical fibres in the neural lobe are homo- or heterolateral can be answered in favour of the first of these two possibilities. Some supraoptical fibres may, however, pass to the contralateral side through the commisural system of the ventral lip. Besides, owing to the somewhat helicoidal course of the infundibular fibres it is possible that a small part of the supraoptical fibres attain a contralateral situation. Nevertheless, we feel that only the study of experimental material with degenerated fibres can solve this problem satisfactorily. In any case we are convinced that no large scale changes in the position of the supraoptical fibres occur in the distal part of the neurohypophysis. It has been said repeatedly that in the proximal part of the neurohypophysis the greater part of the supraoptical fibres, which are ultimately situated in the ventral wall, are first situated in the lateral wall of the infundibulum, after having entered through the lateral lip. This is indeed an important topographical change in the position of the fibres.

In chapter VI we study the histological constitution of the zona palisadica with special reference to the nerve fibres. The existence of nerve fibres in the zona palisadica is supported by this investigation. These fibres are certainly more difficult to stain than those of the central zone of the infundibulum. Confusion with ependyma fibres is not likely owing to the morphological differences between the thick ependyma fibres – running perpendicularly to the fibres of the zona fibrillaris – and the very thin and irregularly running fibres of the zona palisadica. In some cases, however, differentiation between these two sorts of fibres may be a hazardous business. Indeed, often ependyma fibres (which – when stained by neurofibrillar methods – may eventually appear as thin fibres) pierce the basal membrane, separating the infundibular wall from the pars infundibularis, to join the interfollicular connective tissue of the latter. These fibres may easily be taken (and in fact they have been) for nerve fibres which innervate the pars infundibularis. We have tried to avoid this error; those fibres which penetrate into the pars infundibularis are only considered nerve fibres if

their course is typically irregular and contorted and if they remain clearly independent from the connective tissue. The problem is more complicated by the fact that strongly stained supraoptical fibres suddenly leave the zona fibrillaris, and bending approx 90°, penetrate into the zona palisadica where they may end or, continuing their course, they may penetrate into the pars infundibularis. These fibres may easily be taken for ependyma fibres.

No explanation has been found for the intense staining of the background in the zona palisadica. It might be due to the richness of this region in neuroglia fibres, but if this is so, then it is difficult to explain why the zona fibrillaris (which is also very rich in neuroglia fibres) shows such a high degree of contrast between the formed elements and the completely unstained background.

The zona palisadica is very rich in vessels which are surrounded by the perivascular space. Nerve fibres are present close to the vessel-wall but separated from it by the perivascular space. It may be of interest to remark that the ependyma fibres are frequently inserted into the border of the perivascular space, thus establishing a direct connection between the zona ependymalis (and also the liquor cerebrospinalis) and the capillary loops of the infundibulum (fig. 20a). This is especially clear in the central zones of the ventral wall. Nevertheless some parts of the zona palisadica, especially the lateral part of it (fig. 23) are very poor in vessels. It would be a mistake to think that the degree of development of the zona palisadica is proportional to the richness in vessels.

Very clear formations resembling nerve terminals have been found in the zona palisadica. Contrary to what might be expected, these formations are not always clearly related to particular elements (cells, blood vessels). The rôle of these nerve terminals seems difficult to establish. These formations have often been found in the zona palisadica of the lateral wall, i.e., in a part very poor in formed elements. In other cases the nerve terminals were present close to the wall of the vessels. The "endlamellae" seem to be nerve fibres with degenerative characteristics which, in some cases, might give rise to Herring bodies.

It is felt that a great deal more work can be done to ascertain the true signification of the zona palisadica. The contrast between the zona fibrillaris and the zona palisadica is so striking that every attempt at explaining it in terms of the presence of vessels etc. must be quickly dismissed. The use of more resolutive staining methods and the use of the electron microscope might lead to a substantial improvement in our knowledge of this zone.

SUMMARY

This thesis is mainly concerned with the topography and course of the hypothalamic nerve supply of the neurohypophysis. Attention was also paid to more general questions such as microscopic structure and division into parts. The structure, topography and limits of what we call the "zona palisadica" have been also investigated.

In chapter I, an account of the embryological development of the hypophysis of the cat is given. Chapter III deals with the literature on the hypothalamic innervation of the neurohypophysis.

Our observations are given in chapters II, IV, V and VI. In chapter II we deal with the form and relations of the neurohypophysis. This organ is described as consisting of four walls: a ventral, a dorsal and two lateral. It was found that in the proximal part of the neurohypophysis, the four walls have aproximately the same thickness. This part of the neurohypophysis was called infundibulum. It corresponds with what in English and American literature is known as the "median eminence". The neural lobe shows, on the contrary, that its walls are much thicker than its homologues of the infundibulum, with the exception of the dorsal wall which appears to be the continuity of the dorsal wall of the infundibulum. This part is invested by the pars infundibularis of the adenohypophysis (the pars tuberalis of English and American literature) and by the transition zone between the pars distalis and the pars intermedia. The neural lobe is lined by the pars intermedia, except for its dorsal pole, which is covered only by the pia-mater.

The form of the neurohypophysis is described in detail with the help of sagittal and transversal series. The area of insertion of the infundibulum into the tuber cinereum (entrance area) is also studied. This leads to the distinction of four lips (ventral, dorsal and two lateral) which are brought into connection with the homologue walls. The nomenclature of the hypophysis used in this thesis is given in the last page of this chapter.

In chapter IV, three main questions, viz., the microscopic structure of the infundibulum, its line of demarcation with the tuber at one side and with the neural lobe at the other, and the division of the neurohypophysis into parts, are dealt with. Three layers can be distinguished in the infundibular wall: the zona fibrillaris, the zona ependymalis and the zona palisadica. The first two layers together form the "zona interna" because of their intimate relations. These layers can be found also in the dorsal and lateral walls of the infundibulum. The

existence of a fourth layer, described in the dog by other scientists who called it "zona granulosa", has been confirmed in the cat. This fourth layer is restricted to the ventral wall.

The line of demarcation between the tuber cinereum and the infundibulum is not a clear-cut one. Instead, a transition zone occurs in which the tuber overlaps the infundibulum and viceversa. This occurs over a short distance only. The sulcus tuberis infundibularis, together with the termination of the lining of the pars infundibularis is considered the limit between tuber cinereum and neurohypophysis.

It was found that no clear demarcation line exists between the infundibulum and the neural lobe. The central zone of the infundibulum proved to reach as far as the dorsal pole of the neural lobe in a median sagittal section. The tissue characteristic of the neural lobe (Herring's light and dark areas) does not exist in the dorsal wall of the neural lobe which is constituted exclusively by infundibular tissue. The whole extension of the lumen of the recessus into the neural lobe is encircled by the internal zone of the infundibulum. Thus what we call "neural lobe", is a central zone with infundibular characteristics as well as a peripheral zone, which is the neural lobe proper. The latter is always separated from the lumen of the recessus by a layer of tissue which is the central zone of the infundibulum.

A new division of the neurohypophysis, based on the above-mentioned structural facts is proposed. Instead of the current division into "median eminence", "infundibular stem" and "neural lobe", we suggest a division of the whole neurohypophysis into an internal zone, of uniform structure and an external zone, of variable structure. The former consists of the zona ependymalis plus the zona fibrillaris, and the latter consists of the zona palisadica in the proximal part of the neurohypophysis and the zona lobularis in the distal part of it. For the cat at least this division is more strictly in accordance with the facts than the earlier ones.

In chapter V the topography of the hypothalamic nerve supply of the neurohypophysis is studied. Two main fibre-systems are distinguished: the tractus supraoptico-hypophyseus and the tractus tubero-hypophyseus. The former originates in the nucleus supraopticus and paraventricularis. The latter originates in the nuclei of the tuber cinereum. These fibres are always situated more internally than the supraoptical ones. First the topography of the fibres in the entrance area is studied. The ventral, lateral and dorsal lips are taken separatedly. In the former, three main fibre tracts may be distinguished: 1. The periventricular tract which runs parallel to the ventricular wall. 2. The perifornical tract which originates in the neighbourhood of the fornix and descends towards the ventral lip and 3. The supraoptical tract which originates in the nucleus supraopticus. The latter fibres occupy a very lateral and superficial position in the ventral lip. These three fibre-tracts merge in the peripheral part of the ventral lip where they form two

fibre systems: the first is formed by transversal fibres which cross the median line, forming the "commissure of the ventral lip"; it occupies an intermediate position. The second is completely superficial and is constituted by fibres more or less perpendicular to the former ones, being held between the commissural fibres above and the pars infundibularis below. We call this "palisade grouped fibres". It must be understood that this fibre-system has nothing to do with the zona palisadica which does not yet exist at this level.

In the lateral lip of the entrance area the fibres are disposed in two tracts; the supraoptic tract, which occupies a very lateral situation and is in contact with the pars infundibularis without interposition of the zona palisadica, and the periventricular tract, the fibres of which enter the lateral lip, running parallel to the ventricular wall. These fibres originate in the nuclei of the tuber.

The fibres entering the neurohypophysis though the dorsal lip belong to the tubero-hypophyseal tract. Part of these fibres cross the median line of their way to the opposite side of the infundibular wall. The supraoptical fibres do not penetrate into the infundibulum via the dorsal lip. Supraoptical fibres can be found, however, in the dorsal wall of the infundibulum.

The course and position of the hypothalamic fibres inside the infundibulum is next dealt with. A system of transversal fibres situated immediately beneath the zona ependymalis is described. A similar transversal system has been found also in the dorsal wall. The grouping in bundles of the supraoptic fibres in the zona fibrillaris is emphasized. This peculiarity helps us to distinguish the supraoptical fibres from the tuberal ones which run singly. The differences in thickness between the fibres of these two great systems cannot be studied with the light-microscope owing to their exceedingly small diameter. Statements that the supraoptical fibres are thicker than the tuberal ones, in so far as they are not supported by observations with the electron microscope, are incorrect. More than 95% of the infundibular fibres have a thickness of $^1/_2\ \mu$ or even less.

After a close examination of the lateral wall of the infundibulum, we have come to the conclusion that many fibres pass from the dorsal to the ventral wall (or viceversa). This means that the position of a particular axon is not, of necessity, the same along its entire course. Some axons may follow an irregular helicoidal course.

The areas of termination of the hypothalamic fibres are also studied. It is clear that the tuberal fibres do not reach the neural lobe, but remain in the zona palisadica, where they terminate. The supraoptical fibres situated in the ventral wall supply the perivascular spaces of the ventral wall of the neural lobe and also those in the lateral wall of it. Those situated in the dorsal wall of the infundibulum terminate in the lateral wall of the neural lobe. A number of supraoptical fibres may end in the infundibulum, showing Herring bodies.

The tuberal fibres contained in the dorsal wall of the infundibulum pass in great numbers to the ventral wall via the lateral wall. Many tuberal fibres end

also in the zona palisadica of the dorsal wall. The tuberal fibres of the ventral wall terminate in the zona palisadica of the ventral wall where they innervate the capillary loops. It is concluded that the majority of the supraoptical fibres innervating the neural lobe are homolateral. Heterolateral fibres may exist also; they can pass to the opposite side via the commissure of the ventral lip. We think that the heterolateral fibres – if such fibres exist – are not very numerous. A considerable number of the tuberal fibres entering the infundibulum through the dorsal lip are, on the contrary, heterolateral.

A new structural layer in the ventral wall of the infundibulum has been found in Häggqvist series. This fourth layer seems to be rich in connective fibres and in nerve fibres with degenerative characteristics. In conformity with Hagen and Hanström, who have described it earlier in the dog, we call it "zona granulosa".

Countings of the hypothalamic fibres in transversal sections of the narrowest part of the infundibulum have been made. The number of fibres in this zone was found to be 17000 fibres approximately, with a maximum of 17828, and a minimum of 16250. It should be remembered that the tuberal fibres are virtually not included in these numbers since they terminate in more proximal levels. The total number of hypothalamic fibres is, therefore, considerably higher than that indicated by these figures.

In chapter VI the topography of the tractus tubero-hypophyseus and of its termination area (the zona palisadica) is examined. The latter is divided in two parts: the areas rich in vessels and the areas poor in vessels. In the former, special attention is paid to the structure of the perivascular space and to the innervation of the long and short types of capillary loops. In the areas of the zona palisadica poor in vessels, numerous formations which could be taken for nerve terminals are described.

When dealing with the course that the tuberal fibres follow in order to reach their termination areas (the zona palisadica), an important crossing between the two great hypothalamic fibre systems is described. This crossing occurs in the lateral wall of the infundibulum.

In the last pages of this thesis literature data concerning the vascular arrangement of the neural lobe are produced, supporting our division of the neurohypophysis into two zones. We have ourselves observed that the inferior hypophyseal artery gives several ascending branches which closely resemble the typical "capillary loops" of the infundibulum. The internal zone of the neural lobe shows, therefore, a vascularization which can be compared with that of the infundibulum.

RESUMEN

El objetivo primordial de esta tesis (pero no el único) es el estudio detenido de la topografía de las fibras nerviosas hipotalámicas que inervan la neurohipófisis. Macroscópicamente, la neurohipófisis es un órgano impar y medio que recibe fibras procedentes de ambas mitades del hipotálamo; nuestro problema inicial consiste en averiguar si la inervación hipotalámica de la neurohipófisis es fundamentalmente homo ó contralateral. El tema mismo de nuestro estudio nos ha conducido a tratar problemas morfológicos de índole más general como son los siguientes: 1. Forma externa de la neurohipófisis y sus relaciones con las diversas partes de la adenohipófisis que la circundan. 2. Estructura histológica y límites. 3. División en partes con arreglo a su estructura. 4. Topografía y curso de las fibras nerviosas desde su origen a su terminación. 5. Estructura de la zona palisadica.

El material a nuestra disposición está formado por un total de 16 series cortadas en cuatro planos, a saber, sagital, frontal, horizontal y paralelo al eje principal del infundíbulo. Los principales métodos de coloración empleados fueron: Hematoxilina-eosina, violeta de cresilo, Azan, Häggqvist, Bodian y Cajal (fórmula al alcohol amoniacal).

El capítulo II se dedica exclusivamente al estudio de la forma de la neurohipófisis y de sus relaciones con la adenohipófisis. La neurohipófisis del gato se caracteriza por el gran desarrollo que alcanza el recessus infundibularis que llega a penetrar hasta el centro mismo del lóbulo nervioso. Esta disposición nos permite distinguir una pared inferior (que llamamos pared ventral), una pared superior (pared dorsal) y dos paredes laterales, bien visibles en cortes transversales, que cierran a los lados la luz del recessus infundibularis. En conformidad con diversos autores, se acepta el sulcus tuberis infundibularis como límite macroscópico proximal de la neurohipófisis.

Se llama la atención sobre el hecho de que las paredes neurohipofisarias en la parte proximal del órgano son relativamente delgadas, sin que existan grandes diferencias de espesor entre ellas. En cambio, la pared de la porción distal de la neurohipófisis se engruesa mucho alcanzando un espesor varias veces mayor que el de la porción proximal. A la porción terminal engrosada de la neurohipófisis se la conoce con el nombre de lóbulo nervioso ó processus infundibularis. La porción proximal de parades delgadas constituye el infundíbulo. Hay que hacer notar que el engrosamiento de la pared del lóbulo nervioso no es

igual en toda la circunferencia de ésta, sino que la pared ventral y laterales se encuentran mucho más desarrolladas que la pared dorsal. Esta última puede quedar reducida, en el polo dorsal del lóbulo nervioso, a una membrana rudimentaria. En cortes frontales y sagitales podemos comprobar que tanto el suelo como las paredes laterales de la dilatación terminal del recessus infundibularis son tan gruesos en comparación con el techo que la cavidad del recessus ocupa una posición excéntrica, pareciendo estar desviada hacia arriba.

A continuación describimos la forma de la neurohipófisis utilizando para ello series sagitales y frontales. Se hace resaltar el que casi todo el contorno de la neurohipófisis se excuentra revestido por alguna de las diversas regiones que constituyen la adenohipófisis. Así el infundíbulo está revestido por la pars infundibularis y por la porción proximal de la zona de transición entre la pars distalis y la pars intermedia ("nasale Umschlagzone" de Romeis). El lóbulo nervioso se encuentra rodeado por la pars intermedia, excepto en el polo dorsal del órgano, donde no existe revestimiento adenohipofisario. Es de notar que la pars distalis no establece contacto alguno con la neurohipófisis.

En el capítulo IV se estudia en primer lugar la estructura histológica y el límite proximal del infundíbulo. Se pueden distinguir tres capas en esta región que son las siguientes: 1. La más profunda es el epitelio ependimario que limita la luz del recessus infundibularis. A este epitelio le damos el nombre de "zona ependymalis". 2. La capa intermedia está constituída por fibras nerviosas, en su mayoría colocadas más o menos sagitalmente. Numerosas células (pituicitos ó células de la glía) se encuentran también situadas en ésta capa, la cual ha recibido el nombre de "zona fibrillaris" en nuestra nomenclatura. 3. Finalmente, la capa más superficial, que se encuentra ya revestida por la pars infundibularis, presenta una estructura especial, caracterizada por la gran escasez en células y por una gran riqueza en fibras de varias clases (nerviosas, gliales, conjuntivas, ependimarias). A ésta zona periférica la llamamos "zona palisadica" en atención al aspecto que le prestan las numerosas fibras ependimarias que en ella se encuentran. Las zonas 1 y 2 están estrechamente relacionadas y se pueden agrupar bajo el nombre de "zona interna".

El límite entre tuber cinereum e infundíbulo no es abrupto sino que en su lugar existe una zona de transición en la cual están representadas estructuras pertenecientes al tuber y a la neurohipófisis. En efecto, una cuña de células nerviosas que forman parte del nucleus infundibularis (tuber) se introduce entre la zona fibrillaris y la zona ependymalis, separándolas. Al propio tiempo, la zona palisadica desaparece a este nivel, por lo que pared del infundíbulo continúa estando constituída por tres capas. La penetración de células nerviosas en la pared del infundíbulo tiene poca profundidad, agotándose a poca distancia del sulcus tuberis infundibularis que puede aceptarse como frontera entre tuber cinereum y neurohipófisis no sólo macro sino también microscópicamente.

A continuación se pasa a examinar el problema del límite distal del infundíbulo,

es decir, la separación entre el infundíbulo y el lóbulo nervioso. Histológicamente ésta última región está caracterizada por la abundancia en vasos y fibras nerviosas y por la existencia de zonas claras y oscuras dispuestas con cierta regularidad. Ahora bien, si observamos con cuidado el lóbulo nervioso a mediano aumento nos daremos cuenta de que entre el tejido que constituye el lóbulo nervioso propiamente dicho y la luz de la dilatación terminal del recessus infundibularis se interpone una delgada capa de fibras nerviosas dispuestas formando manojos que cursan más ó menos longitudinalmente, que no es sino la prolongación distal de la zona interna del infundíbulo. Hemos podido comprobar, además, que el tejido propio del lóbulo nervioso no existe en la pared dorsal del mismo, al menos en la parte sagital y media. Esta región no es otra cosa que la prolongación de la zona interna del infundíbulo, la cual llega a alcanzar el polo dorsal, rudimentario, del órgano. Ello quiere decir que las paredes ventral y laterales del lóbulo nervioso están constituídas por dos capas: la central, formada por el revestimiento ependimario y por fascículos de fibras nerviosas, que representa la zona interna del infundíbulo y la periférica, constituída por las zonas claras y oscuras de que hemos hecho mención. En cambio, la pared dorsal está formada exclusivamente (en la línea media) por la prolongación de la zona interna del infundíbulo. Aquí no existe tejido propio del lóbulo nervioso. Podemos afirmar pues, que éste tiene significación de zona externa, lo mismo que la zona palisadica. Ahora bien, a pesar de tener numerosos puntos de contacto, la estructura de la última no es igual que la estructura de la primera.

De lo dicho se desprende que es imposible establecer un límite satisfactorio entre el infundíbulo y el lóbulo nervioso dado que ambas estructuras están dispuestas algo así como las escamas de una cebolla. En lugar de la división actual en "eminencia media", "tallo (o pedículo)", y "lóbulo nervioso", nosotros proponemos dividir la neurohipófisis del gato en dos partes: la zona interna, de estructura constante, constituída por la zona fibrillaris + la zona ependymalis y la zona externa, de estructura variable, constituída por la zona palisadica en la parte proximal de la neurohipófisis y por las zonas claras y oscuras (Verdichtungszonen y Zwischenstreifen de Romeis) en la parte distal.

En el capítulo V se estudia la topografía de las fibras hipotalámicas que inervan la neurohipófisis, utilizando de preferencia series transversales. Distinguimos dos grandes grupos de fibras: el tractus supraoptico-hypophyseus, procedente del núcleo del mismo nombre (y en parte, del nucleus paraventricularis) y el tractus tubero-hypophyseus que se origina en distintos núcleos del tuber cinereum. Estas útimas fibras, durante su trayecto en el tuber cinereum, están situadas siempre por dentro de las fibras supraópticas.

En primer lugar estudiamos la topografía de las fibras en el área de entrada, o sea en la zona de inserción del infundíbulo en el tuber. Describimos separadamente la situación de las fibras en el labio ventral, lateral y dorsal del área

de entrada. En el primero, se pueden distinguir tres fascículos principales: 1. El fascículo periventricular que cursa paralelo a la pared del 3er ventrículo y a corta distancia de éste 2. El fascículo perifornical que procede — entre otras — de áreas vecinas al fórnix y se dirige al labio ventral describiendo una curva de convexidad lateral y 3. El fascículo supraóptico que procede en su mayor parte del núcleo del mismo nombre y cuyas fibras ocupan una posición completamente lateral. Estos tres fascículos se reúnen en la porción periférica del labio ventral donde forman dos sistemas de fibras; uno de ellos está constituído por fibras transversales que ocupan una posición intermedia. Estas fibras cruzan la línea media, formando la "comisura del labio ventral". El segundo sistema es completamente superficial, estando formado por fibras más o menos perpendiculares a las anteriores y comprendidas entre el sistema comisural que las limita por encima y la pars infundibularis por debajo. A este grupo (que procede del fascículo periventricular) le llamamos "fibras en empalizada". Esto no tiene nada que ver con la "zona palisadica", que no existe a este nivel.

En el labio lateral del área de entrada, las fibras se disponen en dos fascículos principales: las fibras supraópticas ocupan una posición muy lateral y superficial, hasta el punto de que contactan con la pars infundibularis sin interposición de zona palisadica. El segundo grupo de fibras está formado por el fascículo periventricular cuyas fibras entran en el infundibulo caminando paralelamente a la pared del ventrículo. Estas fibras se originan en gran parte en los núcleos del tuber.

Las fibras que entran en la neurohipófisis por el labio dorsal, pertenecen al tractus tubero-hypophyseus. Parte de estas fibras cruzan la línea media yendo a situarse en la pared dorsal en el lado contrario del que proceden. Las fibras del tractus supraoptico-hypophyseus no utilizan — o lo hacen en muy escaso número — el labio dorsal para ingresar en la neurohipófisis. A pesar de ello, numerosas fibras supraópticas se encuentran en la pared dorsal. Queremos hacer resaltar que, además de las fibras supraópticas, un gran número de fibras tuberales toman parte en la inervación de la neurohipófisis.

A continuación se pasa a estudiar el curso de las fibras en el infundíbulo. Describimos un sistema de fibras transversales en la mitad proximal del mismo, situado inmediatamente por debajo del epéndima. La gran mayoría de las fibras son sagitales, estando separadas de la pars infundibularis por la zona palisadica. En la pared dorsal describimos asimismo un grupo de fibras transversales, situadas inmediatamente por encima del epéndima. El curso ulterior de estas fibras es difícil de establecer. Se hace hincapié en que las fibras del tractus supraóptico-hypophyseus van dispuestas en manojos apretados que constan en algunos casos hasta de 16 fibras. Por el contrario, las fibras del tractus tubero-hypophyseus cursan aisladas. Esta diferencia y el hecho de que las impregnaciones argénticas tiñen las fibras del tuber en tonos más claros, es lo único que nos permite distinguir ambos grandes sistemas de fibras en series de cortes coloreadas por la

plata. No existen diferencias de grosor claramente apreciables — al microscopio corriente — entre los cilindroejes del tractus supraoptico- y los del tractus tubero-hypophyseus.

Estudiando las fibras contenidas en la pared lateral del infundíbulo hemos podido comprobar que muchas de ellas pasan de la pared ventral a la dorsal ó viceversa. Ello quiere decir que los axones en el infundíbulo no gozan de una posición fija e inmutable, mejor dicho, que la posición de un cilindroeje determinado no es necesariamente le misma a lo largo de todo su trayecto. Algunos axones poseerían un curso irregularmente helicoidal.

Finalmente nos ocupamos de las áreas de terminación de las fibras hipotalámicas en la neurohipófisis. Examinando a gran aumento la porción más estrecha del infundíbulo, es decir, la desembocadura del infundíbulo en el lóbulo nervioso, observamos que todas las fibras aquí presentes están agrupadas formando manojos los cuales siguen un curso muy regular. Esto nos permite afirmar que se trata de fibras supraópticas. Podemos afirmar que la totalidad de las fibras hipotalámicas que alcanzan el lóbulo nervioso proceden del núcleo supraóptico (y en parte del paraventricularis). Las fibras del tuber se terminan en el infundíbulo, sin llegar a alcanzar el lóbulo nervioso. Una pequeña parte de las fibras supraópticas se terminan también en el infundíbulo bajo la forma de corpúsculos de Herring.

Ahora podemos preguntarnos: ¿cual es el lugar de distribución de las fibras contenidas en la pared ventral, dorsal y laterales del infundíbulo? Para contestar esta pregunta hay que distinguir claramente entre las fibras del tractus supraoptico- y las del tubero-hypophyseus. Las primeras se extienden — en su gran mayoría — desde el núcleo del mismo nombre hasta el lóbulo nervioso donde acaban, bien en la periferia, bien dentro del espacio perivascular (zonas oscuras, Verdichtungszonen de Romeis). Las fibras supraópticas situadas en la pared ventral del infundíbulo se terminan en la pared ventral del lóbulo nervioso y, en parte, en su pared lateral. Las contenidas en la pared dorsal, se distribuyen en los espacios perivasculares de la pared lateral del lóbulo nervioso. Parte de estas fibras dorsales pueden pasar a la pared ventral (o viceversa) en niveles más proximales mediante la pared lateral del infundíbulo.

Las fibras del tractus tubero-hypophyseus contenidas en la pared dorsal del infundíbulo pasan en gran número a la pared ventral, siguiendo el camino que les ofrece la pared lateral. Las restantes, termínanse en la zona palisadica de la pared dorsal.

Las fibras tuberales contenidas en la pared ventral del infundíbulo se agotan en la zona palisadica donde se encargan de la inervación de los glomérulos vasculares nacidos de la riquísima red vascular de la pars infundibularis. Tanto las fibras tuberales de la pared dorsal como las de la pared ventral penetran en la pars infundibularis a la que inervan. La impregnación de estas fibras cesa a corta distancia de atravesar la membrana basal limitante entre ambos territorios.

Se llega a la conclusión de que mayoría de las fibras supraópticas que inervan el lóbulo nervioso son homolaterales. Es posible que existan también fibras heterolaterales que hayan cruzado la línea media por medio de la comisura del labio ventral del área de entrada. Creemos que estas fibras heterolaterales — en caso de existir — no son muy numerosas. Por el contrario, gran parte de las fibras del tuber cinereum que entran en el infundíbulo por el labio dorsal son contralaterales.

En series coloreadas por el método de Häggqvist hemos comprobado la existencia de una cuarta capa en la pared ventral del infundíbulo. Esta nueva capa está situada entre la zona palisadica y la pars infundibularis; los métodos de coloración empleados permiten afirmar que esta zona es rica en fibras conjuntivas. Hay razones para pensar que las fibras nerviosas que puedan encontrarse en esta capa presentan caracteres degenerativos. En conformidad con Hanström y Hagen quienes han descrito esta capa en el perro, le damos el nombre de "zona granulosa".

Se han realizado recuentos, en series transversales, del número de fibras hipotalámicas contenidas en el infundíbulo. Con objeto de conseguir la mayor exactitud posible en los resultados, los recuentos se verificaron en la región más estrecha del infundíbulo; de este modo las fibras se seccionan perpendicularmente al plano de corte. La cantidad encontrada fué de 17000 aprox. con unos valores máximo y mínimo de 17828 y 16250.

En el capítulo VI se estudia la topografía del tractus tubero-hypophyseus y de su área de terminación, la zona palisadica. También estudiamos, mediante impregnaciones argénticas, la estructura fina de ésta zona. El capítulo contiene cuatro puntos: 1. Estructura de la zona palisadica con especial referencia a sus elementos nerviosos. 2. Límite proximal de la misma. 3. Topografía de la zona. 4. Curso de las fibras del tractus tubero-hypophyseus en el infundíbulo.

La zona palisadica puede dividirse en dos grandes zonas de una estructura algo distinta según su mayor ó menor riqueza vascular. En efecto, la zona palisadica de la pared lateral del infundíbulo es pobre en vasos, mientras que la pared ventral — sobre todo a ambos lados de la línea media — es extraordinariamente vascular. La pared dorsal es menos rica en vasos que la ventral pero no está desprovista de ellos. La presencia de los vasos ejerce una gran influencia sobre la estructura de la región por lo que creemos juistificado dividirla en a) areas ricas y b) areas pobres en vasos.

Lo que más llama la atención en la zona palisadica de la pared ventral son los glomérulos capilares que, originándose en una red arterial situada entre el infundíbulo y la pars infundibularis (el Mantelplexus de Romeis) penetran en el espesor de la pared. La mayoría de éstos glomérulos no van más allá de la zona palisadica (glomérulos de tallo corto), pero hay otros que sobrepasan la zona palisadica, llegando a alcanzar la zona ependymalis (glomérulos de tallo largo). Estos glomérulos están rodeados por un espacio perivascular, cuya estruc-

tura parece ser la siguiente: alrededor del endotelio vascular encontramos un espacio que se colorea muy difícilmente, que parece estar constituído por prolongaciones de células neuróglicas que se tiñen difusamente con el Azan y posiblemente por alguna substancia coloide. Sumergidas en este espacio, encontramos fragmentos de fibras nerviosas, en escaso número, que parecen presentar caracteres degenerativos. A su vez, éste espacio está rodeado por un acúmulo de fibras nerviosas pálidas, pertenecientes al tractus tubero-hypophyseus.

Las áreas pobres en vasos muestran una gran abundancia en fibras nerviosas muy finas y pálidas muchas de las cuales parece que se dirigen hacia la pared ventral (o viceversa). Se han encontrado numerosas formaciones que pueden tomarse como terminaciones nerviosas; estas formaciones terminales afectan la forma de anillos, mazas, botones, y formaciones semejantes a lo que Tello llamó "mazas deshilachadas". Estas formaciones pueden interpretarse como la expresión morfológica de la terminación de las fibras del tractus tubero-hypophyseus.

Al tratar del curso que siguen las fibras tuberales que marchan hacia la zona palisadica, se describe un importante cruzamiento entre las fibras de los dos grandes sistemas hipotalámicos que tiene lugar en la parte proximal de la pared lateral del infundíbulo. Las fibras tuberales contralaterales que han penetrado en el infundíbulo a través del labio dorsal del área de entrada parecen dirigirse en parte, hacia la zona palisadica de la pared ventral.

Las últimas páginas de este trabajo se dedican a demostrar, mediante argumentos sacados principalmente de la literatura, que la disposición de los vasos en el lóbulo nervioso presta apoyo a nuestra división de la neurohipófisis en zona externa y zona interna. Como observación personal damos a conocer que hemos visto a la arteria hipofisaria inferior dar ramos que ascienden hacia la luz del recessus infundibularis, de un modo muy semejante a los glomérulos capilares del infundíbulo. La zona interna del lóbulo nervioso tendría pues, una vascularización en todo comparable a la zona interna del infundíbulo.

SAMENVATTING

Het oorspronkelijke, zij het niet het enige, doel van dit proefschrift was de nauwkeurige topografische bestudering van de zenuwvezels uit de hypothalamus, welke de neurohypophyse innerveren. Makroskopisch is de neurohypophyse een enkelvoudig, mediaan gelegen orgaan, dat vezels ontvangt uit beide helften van de hypothalamus. Ons eerste probleem berust op de vraag of de hypothalamische innervatie van de neurohypophyse fundamenteel homo-, hetero- of bilateraal is. Het thema van onze studie heeft ons er onvermijdelijk toe gebracht ook andere morphologische vraagstukken betreffende de hypophyse te behandelen zoals de volgende: 1. De uitwendige vorm van de neurohypophyse en zijn betrekkingen tot de verschillende delen van de adenohypophyse, welke er omheen liggen. 2. De histologische structuur en begrenzing. 3. De verdeling in overeenkomstig gestructureerde onderdelen. 4. De topografie en loop van de zenuwvezels vanaf de oorsprong tot de eindigingen ervan. 5. De structuur van de „zona palisadica".

Het materiaal waarover wij beschikken bestaat uit in totaal 16 series, gesneden in 4 richtingen en wel sagittaal, frontaal, horizontaal en een scheve richting evenwijdig aan de hoofdas van het infundibulum. De voornaamste kleurmethoden, waarvan wij ons bedienden, waren: Haematoxyline-eosine, Cresylviolet, Azan en de kleuringen volgens Häggqvist, Bodian en Cajal.

In hoofdstuk I wordt een kort overzicht van de vroege embryonale ontwikkeling van de neurohypophyse gegeven.

Hoofdstuk II is uitsluitend gewijd aan de bestudering van de vorm van de neurohypophyse en zijn relatie tot de adenohypophyse. De neurohypophyse van de kat wordt gekenmerkt door de hoge graad van uitbreiding die de recessus infundibularis bereikt, welke zelfs doordringt tot in het centrum van de lobus nervosus. Deze toestand veroorlooft ons een onderste wand te onderscheiden (die wij de ventrale wand noemen), een bovenste (dorsale) wand en twee laterale wanden, welke goed zichtbaar zijn in transversale coupes en die zijdelings het lumen van de recessus infundibularis omsluiten. In overeenstemming met verschillende auteurs wordt als makroskopisch zichtbare, proximale begrenzing van de neurohypophyse de sulcus tuberis infundibularis aangenomen.

De aandacht wordt gevestigd op het feit, dat de wanden van de neurohypophyse in het proximale deel van het orgaan betrekkelijk dun zijn zonder dat er onderling groot verschil in dikte bestaat. Daarentegen wordt de wand van het distale deel van de neurohypophyse veel dikker en deze bereikt een afmeting, welke ver-

schillende malen groter is dan die van het proximale deel. Het terminale, verdikte deel van de neurohypophyse wordt onderscheiden door de naam lobus nervosus of processus infundibularis. De opmerking moet gemaakt worden, dat de verdikking van de wand van de lobus nervosus niet gelijkmatig is, maar dat de ventrale en laterale wanden veel meer ontwikkeld zijn dan de dorsale wand. De laatste kan gereduceerd zijn tot een rudimentair vlies, gelegen aan de dorsale pool van de lobus nervosus. In frontale en sagittale coupes kunnen wij vaststellen, dat de bodem evenzeer als de laterale wanden van de in zijn terminale deel uitgezette recessus infundibularis zó dik zijn, vergeleken met het dak, dat de holte van de recessus een excentrische positie inneemt en als het ware naar boven is afgeweken.

Hierna beschrijven wij de vorm van de neurohypophyse. Men moet nadrukkelijk vaststellen, dat bijna de gehele omtrek van de neurohypophyse bekleed wordt door delen, die behoren tot de adenohypophyse. Zo wordt het infundibulum bekleed door de pars infundibularis en door het proximale deel van de overgangszône tussen de pars distalis en de pars intermedia („nasale Umschlagzone" van Romeis). De lobus nervosus wordt omringd door de pars intermedia, behalve aan de dorsale pool van het orgaan, waar een bekleding door de adenohypophyse niet bestaat. Men dient te bedenken, dat de pars distalis geen enkel contact bezit met de neurohypophyse.

Terwijl hoofdstuk III bestaat uit een literatuuroverzicht, worden in hoofdstuk IV de histologische structuur en de begrenzing van het infundibulum behandeld. Men kan aan de neurohypophyse de volgende drie lagen onderscheiden:

1. De zona ependymalis. Deze naam geven wij aan de diepste laag, welke bestaat uit het ependym, dat de holte van de recessus infundibularis begrenst.

2. De zona fibrillaris. Dit is de middelste laag, samengesteld uit zenuwvezels, die merendeels min of meer sagittaal geplaatst zijn; talrijke cellen (pituicyten of gliacellen) zijn ook in deze mantel gelegen.

3. De zona palisadica. Deze, door ons zo genoemde oppervlakkige laag, bekleed door de pars infundibularis, bezit een bijzondere structuur, die gekenmerkt wordt door grote armoede aan cellen en rijkdom aan vezels van allerlei soort (zenuw-, glia-, bindweefsel- en ependymvezels). Wij zijn tot deze naamgeving gekomen op grond van het aspect, dat de talrijke ependymvezels, die wij hier aantreffen, er aan verlenen.

De zones 1 en 2 zijn nauw verwant en kunnen onder de naam „zona interna" samengenomen worden.

De grens tussen tuber cinereum en infundibulum is niet scherp, maar in plaats daarvan is er een overgangsgebied, waarin structuren voorkomen die tot het tuber én tot de neurohypophyse behoren. Een wig van zenuwcellen, die deel uitmaken van de nucleus infundibularis (tuber cinereum), dringt in tussen de zona fibrillaris en de zona ependymalis, de laatste daarbij van elkaar scheidend. Tegelijkertijd verdwijnt op dit niveau de zona palisadica, waardoor de wand van

het infundibulum blijft bestaan uit drie mantels. Het binnendringen van de zenuwcellen in de wand van het infundibulum gaat weinig diep en houdt, niet alleen makro- maar ook mikroskopisch, op korte afstand van de sulcus tuberis infundibularis, die men kan beschouwen als grens tussen tuber cinereum en infundibulum, op.

Vervolgens wordt overgegaan tot het onderzoek van het probleem van de distale grens van het infundibulum, d.w.z. de scheiding tussen infundibulum en lobus nervosus. Histologisch wordt dit laatste gebied gekenmerkt door een overvloed aan vaten en zenuwvezels en door het bestaan van met zekere regelmaat gerangschikte lichte en donkere zônes. Indien wij zorgvuldig de lobus nervosus bekijken met middelmatige vergroting, zullen wij ons bewust worden van het feit dat tussen het weefsel, dat de eigenlijke lobus nervosus vormt, en de holte van de terminale verwijding van de recessus infundibularis een dunne mantel van zenuwvezels ligt, gerangschikt in bundels welke meer of minder longitudinaal lopen en welke niet anders zijn dan de distale uitlopers van de zona interna van het infundibulum. Wij hebben bovendien kunnen vaststellen, dat het eigenlijke weefsel van de lobus nervosus niet voorkomt in de dorsale wand ervan, tenminste niet in het mediane deel. Dit gebied is niet anders dan de voortzetting van de zona interna van het infundibulum, welke er in slaagt de rudimentaire dorsale pool van het orgaan te bereiken. Dit wil zeggen, dat de ventrale en laterale wanden van de lobus nervosus zijn samengesteld uit twee mantels: de centrale, gevormd door de ependymbekleding en door bundels zenuwvezels, welke de zona interna van het infundibulum voorstellen, en de perifere mantel, opgebouwd uit lichte en donkere zônes, die wij reeds vermeld hebben. Anderzijds wordt de dorsale wand van de lobus nervosus in de mediaanlijn uitsluitend gevormd door de voortzetting van de zona interna van het infundibulum. Hier vindt men geen eigen weefsel van de lobus nervosus. Wij kunnen dus vaststellen, dat dit laatste de betekenis heeft van zona externa, te vergelijken met de zona palisadica. Echter, ondanks het feit dat deze twee vele punten van overeenkomst hebben, is de structuur van de laatste niet gelijk aan die van de eerste.

Uit het voorgaande laat zich afleiden, dat het onmogelijk is een bevredigende grens te trekken tussen infundibulum en lobus nervosus omdat beide strukturen enigszins zijn gerangschikt als de rokken van een ui. In plaats van de gebruikelijke verdeling van de neurohypophyse in „eminentia mediana", „steel", en „lobus nervosus", stellen wij voor de neurohypophyse van de kat in twee delen te verdelen: de *zona interna,* een constante struktuur, gevormd door de zona fibrillaris plus zona ependymalis, èn de *zona externa,* van een variabele struktuur, gevormd door de zona palisadica in het proximale deel van de neurohypophyse en door de zona lobularis („Verdichtungszonen und Zwischenstreifen" van Romeis) in het distale deel.

In hoofdstuk V wordt de topografie van de hypothalamische vezels, welke de

neurohypophyse van het begin tot het einde innerveren, bestudeerd; hiervoor werd bij voorkeur gebruik gemaakt van transversaal gesneden series. Wij onderscheiden twee grote groepen van vezels: de tractus supraoptico-hypophyseus, voortkomend uit de kern van dezelfde naam (en deels uit de nucleus paraventricularis) en de tractus tubero-hypophyseus, welke ontspringt in verschillende kernen van het tuber. Gedurende hun loop in het tuber cinereum liggen deze laatste vezels steeds dichter bij de ventrikel dan de vezels van de tractus supraoptico-hypophyseus.

In de eerste plaats bestuderen wij de topografie van de vezels in het areaal waar zij binnentreden, d.w.z. in het gebied waar het infundibulum a.h.w. aan het tuber insereert. Wij beschrijven afzonderlijk de ligging van de vezels in de ventrale, de laterale en de dorsale wand of lip van het intree-areaal. In de eerste kan men drie hoofdbundels onderscheiden: 1. De tractus periventricularis, welke evenwijdig aan en op korte afstand van de wand van de 3e ventrikel loopt. 2. De tractus perifornicalis, die o.a. afkomstig is uit gebieden in de buurt van de fornix en koers zet naar de ventrale wand, ondertussen een boog beschrijvend met lateraalwaarts gerichte convexiteit. 3. De tractus supraopticus, welke voor het grootste deel voortkomt uit de kern van dezelfde naam en waarvan de vezels volledig lateraal gelegen zijn. Deze drie bundels verenigen zich in het perifere deel van de ventrale lip waar zij twee vezelsystemen vormen; één ervan wordt opgebouwd uit transversale vezels, welke een middenpositie innemen. Deze vezels kruisen de mediaanlijn en vormen zo de „commissuur van de ventrale lip". Het tweede systeem ligt geheel oppervlakkig en wordt gevormd door vezels, welke min of meer loodrecht gericht zijn op de eerder genoemde; zij worden gevat tussen het commissuursysteem, dat hen aan de bovenzijde, en de pars infundibularis, die hen aan de onderzijde begrenst. Deze groep (die voortkomt uit de tractus periventricularis) noemen wij „palisade-vezels". Dit heeft niets te maken met de „zona palisadica", die op dit niveau niet voorkomt.

In de laterale lip van het intree-areaal rangschikken de vezels zich in twee hoofdbundels. De supraoptische vezels nemen een uiterst lateraal en oppervlakkig gelegen plaats in, zó zeer dat zij contact maken met de pars infundibularis zonder dat er zona palisadica tussen ligt. De tweede groep wordt gevormd door de tractus periventricularis, waarvan de vezels het infundibulum evenwijdig aan de wand van de ventrikel binnentreden. Deze vezels zijn voor een groot deel afkomstig uit de kernen van het tuber.

De vezels, die de neurohypophyse binnenkomen door de dorsale lip, behoren tot de tractus tubero-hypophyseus. Een deel van deze vezels kruist de mediaanlijn en neemt plaats in het contralaterale deel van de dorsale wand. De vezels van de tractus supraoptico-hypophyseus benutten niet — of misschien in uiterst gering aantal — de dorsale lip om de neurohypophyse binnen te dringen. Wij zouden met nadruk willen opmerken, dat — behalve supraoptische vezels — een groot aantal vezels, afkomstig uit het tuber, deelneemt aan de innervatie van

de neurohypophyse.

Vervolgens wordt overgegaan tot de bestudering van de loop der vezels in het infundibulum. Wij beschrijven een systeem van transversale vezels in de proximale helft ervan, onmiddellijk onder het ependym gelegen. Het eindverloop van deze vezels is moeilijk vast te stellen. Men moet de nadruk leggen op het feit, dat de vezels van de tractus supraoptico-hypophyseus gerangschikt zijn in samengedrukte bundels, welke in enkele gevallen wel 16 vezels bevatten. Daarentegen lopen de vezels van de tractus tubero-hypophyseus geïsoleerd. Dit verschil en het feit, dat zilverimpregnaties de vezels van het tuber kleuren in meer heldere tonen, is het enige, dat ons veroorlooft een differentiatie te maken tussen de twee grote vezelsystemen in series van met zilver gekleurde coupes. Er bestaan geen duidelijk te waarderen verschillen in dikte — licht-mikroskopisch — tussen de ascylinders van de tractus supraoptico- en die van de tractus tubero-hypophyseus.

Bij de bestudering van de vezels in de laterale wand van het infundibulum hebben wij kunnen vaststellen, dat vele ervan overgaan van de ventrale wand naar de dorsale of omgekeerd. Dit wil zeggen, dat de axonen van het infundibulum niet een vaste onveranderlijke ligging hebben, zodat de positie van een bepaalde ascylinder niet noodzakelijk langs zijn hele traject dezelfde is. Enkele axonen zouden een onregelmatig schroefvormige loop hebben.

Tenslotte houden wij ons bezig met die gebieden waar de hypothalamische vezels in de neurohypophyse eindigen. Bij het onderzoek met grote vergroting van het smalste deel van het infundibulum, d.w.z. de overgang van het infundibulum in de lobus nervosus, nemen wij waar, dat alle hier aanwezige vezels in de vorm van bundels zijn gegroepeerd, welke een zeer regelmatige weg volgen. Dit veroorlooft ons te besluiten, dat het hier gaat om supraoptische vezels. Wij kunnen vaststellen, dat alle hypothalamische vezels, welke de lobus nervosus bereiken, uit de nucleus supraopticus (en deels uit de nucleus paraventricularis) komen. De vezels van het tuber eindigen in het infundibulum zonder er in te slagen de lobus nervosus te bereiken. Een klein deel van de supraoptische vezels eindigt ook in het infundibulum in de vorm van de lichaampjes van Herring.

Bij de beantwoording van de vraag, hoe het verdelingspatroon is van de vezels, die liggen in de ventrale, dorsale en laterale wanden van het infundibulum, moet men duidelijk onderscheid maken tussen de vezels van de tractus supraopticus en die van de tractus tubero-hypophyseus. De eerste strekken zich uit vanaf de kern van dezelfde naam tot aan de perivasculaire ruimten (donkere zônes) van de zona lobularis. De supraoptische vezels, in de ventrale wand van het infundibulum gelegen, eindigen in de ventrale wand van de lobus nervosus en deels in de laterale wand ervan. De vezels in de dorsale wand verdelen zich over de perivasculaire ruimten van de laterale wand van de lobus nervosus. Een deel van deze dorsale vezels kan op meer proximale niveau's overgaan naar de

ventrale wand (of omgekeerd), dóór de laterale wand van het infundibulum heen.

De vezels van de tractus tubero-hypophyseus, gelegen in de dorsale wand van het infundibulum, gaan in groten getale over in de ventrale wand, de weg volgend welke de laterale wand hun biedt. De overige eindigen in de zona palisadica van de dorsale wand. De tuberale vezels, welke in de ventrale wand van het infundibulum voorkomen, verliezen zich in de zona palisadica, waar zij de innervatie van de vaatkluwens uit het zeer rijke vaatnet van de pars infundibularis verzorgen. Zowel de tuberale vezels van de dorsale wand als die van de ventrale wand dringen door tot in de pars infundibularis, welke zij innerveren. De impregnatie van deze vezels houdt op op korte afstand van het punt waar zij de basale grensmembraan tussen beide gebieden doorboren.

De conclusie wordt gemaakt, dat de meerderheid van de supraoptische vezels, die de lobus nervosus innerveren, homolateraal zijn. Het is mogelijk dat er ook heterolaterale vezels voorkomen, welke de mediaanlijn gekruist hebben in de commissuur van de ventrale lip in het intree-areaal. Wij geloven, dat deze heterolaterale vezels — in het geval dat zij bestaan — niet zeer talrijk zijn. Daarentegen zijn een groot deel van de vezels uit het tuber cinereum, die het infundibulum door de dorsale lip binnenkomen, contralateraal.

In series, gekleurd volgens de methode van Häggqvist, hebben wij het bestaan geconstateerd van een vierde mantel in de ventrale wand van het infundibulum. Deze nieuwe laag is gelegen tussen de zona palisadica en de pars infundibularis; de gebruikte kleurmethoden veroorloven vast te stellen, dat deze zone rijk is aan bindweefselvezels. Er zijn redenen om te denken, dat de zenuwvezels, die in deze mantel aangetroffen kunnen worden, kenmerkende degeneratieverschijnselen vertonen. In overeenstemming met Hanström en Hagen, die deze laag bij de hond beschreven hebben, geven wij daaraan de naam „zona granulosa".

Er zijn enkele tellingen uitgevoerd in transversale coupes van het aantal vezels, welke in het infundibulum voorkomen. Met de bedoeling, de grootst mogelijke nauwkeurigheid te bereiken in de resultaten, werden de tellingen uitgevoerd in het smalste gebied van het infundibulum; op deze wijze worden de vezels loodrecht op het vlak van de coupe getroffen. Gevonden werd, dat ongeveer 17000 vezels in de lobus nervosus binnendringen.

In hoofdstuk VI wordt de topografie beschreven van de tractus tubero-hypophyseus en van het gebied waar deze eindigt, de zona palisadica. Ook bestudeerden wij door middel van zilver-impregnaties de fijne structuur van deze zone.

De zona palisadica kan verdeeld worden in twee zônes, waarvan de structuren enigszins onderscheiden kunnen worden door de meerdere of mindere rijkdom aan vaten. De zona palisadica van de laterale wand van het infundibulum is arm aan vaten, terwijl de ventrale wand, bovenal aan weerszijden van de mediaanlijn, uitzonderlijk rijk gevasculariseerd is. De dorsale wand is minder rijk aan vaten dan de ventrale maar is er niet van verstoken. De aanwezigheid van de vaten beïnvloedt in sterke mate de structuur van het gebied,

waardoor wij ons gerechtigd achten het te verdelen in gebieden, rijk aan vaten, en gebieden, arm aan vaten.

Wat meer de aandacht trekt in de zona palisadica van de ventrale wand zijn de vaatkluwens, die, voortkomend uit een arteriëel net, tussen het infundibulum en de pars infundibularis gelegen (de Mantelplexus van Romeis), in de dikte van de wand doordringen. De meerderheid van deze kluwens gaan niet verder dan de zona palisadica (glomeruli met korte steel), maar er zijn andere, die de zona palisadica overschrijden, er zo in slagende de zona ependymalis te bereiken (glomeruli met lange steel). Deze glomeruli zijn omringd door een perivasculaire ruimte, die de volgende structuur blijkt te bezitten: rondom het vaatendotheel ontmoeten wij een ruimte, die zich moeilijk laat kleuren; deze schijnt uitlopers van neurogliacellen te bevatten, welke zich met de azan-methode diffuus kleuren, en mogelijk een of andere „colloide" substantie. Ingebed in deze ruimte treffen wij fragmenten van zenuwvezels aan — in een schaars aantal — die degeneratieve kenmerken schijnen te bezitten. Op zijn beurt is deze ruimte omhuld door een opeenhoping van bleke zenuwvezels, die behoren tot de tractus tubero-hypophyseus.

De vaatarme gebieden bezitten een overvloed van zeer fijne en bleke zenuwvezels, waarvan vele naar de ventrale wand koers schijnen te zetten (of omgekeerd). Wij hebben talrijke vormsels aangetroffen, die als zenuweindigingen beschouwd kunnen worden; deze eindigingen nemen de vorm aan van ringen, staafjes, knoppen en vormsels, die lijken op wat Tello noemt „uitgerafelde staafjes". Deze vormsels moet men mogelijkerwijs interpreteren als de morphologische weergave van het eindigen der vezels van de tractus tubero-hypophyseus.

Met betrekking tot de weg, die de tuberale vezels volgen op weg naar de zona palisadica, wordt een belangrijke kruising beschreven tussen de vezels van de twee grote hypothalamische systemen, die plaats vindt in het proximale deel van de laterale wand van het infundibulum. De tuberale vezels, die het infundibulum door de dorsale lip van het intree-areaal zijn binnengedrongen, schijnen voor een deel zich te begeven naar de zona palisadica van de ventrale wand.

De laatste pagina's van dit werk zijn gebruikt om aan te tonen, door middel van hoofdzakelijk uit de literatuur geputte argumenten, dat de rangschikking van de vaten in de lobus nervosus steun verleent aan onze verdeling van de neurohypophyse in een zona interna en een zona externa. Als persoonlijke waarneming vermelden wij, dat wij de a. hypophysea inferior takken hebben zien afgeven, die opstijgen naar het lumen van de recessus infundibularis, op een wijze die veel lijkt op de capillairkluwens van het infundibulum. De zona interna van de lobus nervosus zou dan een vascularisatie hebben, die in alle opzichten vergelijkbaar is met die van de zona interna van het infundibulum.

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STELLINGEN.

1. De door ons in dit proefschrift beschreven commissuur in de ventrale wand van het begin van het infundibulum dient scherp te worden onderscheiden van de commissuren van MEYNERT en GANSER.

2. Op grond van zijn morfologische structuur mag de hypothalamus niet als een homogeen onderdeel van de hersenen worden beschouwd.

3. In de neurologische diagnostiek dient bij corticale afwijkingen onderscheid te worden gemaakt tussen het „centrale" en het „periphere" syndroom. (J. GONZALO: "Investigaciones sobre la nueva dinámica cerebral", Madrid, 1945).

4. De opvatting, dat het hyaluronzuur door de mestcellen zou worden gevormd, is gebaseerd op onjuiste interpretatie van waarnemingen.

5. Bij het vinden van een schildklierknobbel op jeugdige leeftijd houde men rekening met de mogelijkheid van een cystopapillair carcinoom in aansluiting op een Röntgen-bestraling van de hals in de kinderjaren.

6. Het is waarschijnlijk, dat de kwantitatieve waarnemingen van SMITH over de spanningen, die in weke delen om bepaalde gewrichten tijdens een beweging ontstaan, van betekenis zijn voor de klinische benadering van rheumatische aandoeningen.

7. De invloed van het licht op de ontwikkeling der geslachtsfuncties bij warmbloedige dieren kan niet verklaard worden uit de aanwezigheid van thans bekende zenuwverbindingen.

P. MARTINEZ MARTINEZ